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Gastroesophageal Reflux

Presented by-Maj. Ronald Szjkowski, USA, MC

Dr. Szjkowski was unable to provide a clinical summary of gastroesophageal reflux disease. The following review by Dr. Joel Richter is provided for your review and was obtained from the ASGE web page (www.asge.org/doc/116)

GASTROESOPHAGEAL REFLUX DISEASE

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Gastroesophageal reflux, along with its major symptom, heartburn, is the most common disorder of the esophagus, the major indication for consumption of antacids, and probably the most prevalent clinical condition originating from the gastrointestinal tract. Gastroesophageal reflux disease (GERD) is defined as the sequela, both clinical and histopathologic, of the movement of gastroduodenal contents into the esophagus. GERD is a spectrum of disease. Healthy persons will intermittently have "physiologic" reflux that occurs after meals, is associated with multiple short episodes of acid reflux, does not occur at night, and is usually asymptomatic. On the other hand, more frequent and prolonged episodes of acid reflux may be "pathologic" and lead to symptoms and mucosal injury, that is, "reflux esophagitis."

EPIDEMIOLOGY

Epidemiologic studies show that approximately 14% of the U.S. population experiences heartburn or acid regurgitation weekly and 7% experience symptoms daily.1 However, most patients with symptoms of GERD do not seek medical attention. More than 40% take antacids for their heartburn, but only one in four patients has discussed this complaint with his or her physician.

Although heartburn and esophagitis are often considered together, this may not be the case. Endoscopic surveys of patients with reflux symptoms show that only 40% to 65% have erosive or ulcerative esophagitis.2 Fortunately, most of these patients have mild or moderate forms of esophagitis; less than 15% have severe ulcerative esophagitis. The prevalence of GERD and esophagitis increases dramatically in the elderly. One study reported severe esophagitis in 21% of patients who were more than 65 years of age compared with an incidence of only 5% in patients younger than 64 years.3

The esophageal complications of GERD include Barrett's esophagus, esophageal ulcerations, bleeding, perforation, and esophageal stricture. In addition, extra esophageal manifestations of GERD are increasingly being reported and include pharyngitis, laryngitis, asthma, bronchitis, and non-cardiac chest pain. These "atypical" manifestations may be particularly difficult to diagnose because relatively few if any common symptoms of heartburn, acid regurgitation, or dyspepsia are present and because esophagitis is uncommon.

PATHOPHYSIOLOGY

The pathophysiology of GERD results from a complex interplay of several factors including the reflux barrier provided by the lower esophageal sphincter (LES) and crural diaphragm, the ability of the esophagus to clear refluxed material, the volume of gastric contents, intrinsic resistance to injury of the esophageal epithelium, and the presence of a hiatal hernia.4

CLINICAL MANIFESTATIONS

Heartburn is the classic symptom of GERD, but associated complaints include dysphagia, odynophagia, regurgitation, water brash, and belching. Patients describe their heartburn as a retrosternal burning pain that may be noted in the epigastrium, neck, throat, and occasionally in the back. It usually occurs postprandially, particularly after consumption of spicy foods, citrus foods, fats, chocolate, and alcohol. Recumbency and the act of bending over may exacerbate heartburn. Dysphagia usually occurs in the setting of long-standing heartburn, with slowly progressive dysphagia for solids followed by dysphagia for liquids. The most common cause is a peptic stricture, but other causes include severe esophageal inflammation alone, peristaltic dysfunction seen with severe esophagitis, and esophageal cancer that develops from Barrett's esophagus. The presence of odynophagia usually indicates ulcerative esophagitis. The effortless regurgitation of acidic fluids, especially postprandially and when exacerbated by stooping or recumbency, is highly suggestive of GERD. Water brash is the sudden appearance in the mouth of a slightly sour or salty fluid from the salivary glands in response to intraesophageal acid exposure. Excessive belching, probably initiated by increased swallowing of saliva and air brought about by Gastroesophageal reflux, may be an important symptom in some patients.

In contrast, some patients with GERD have no symptoms. This may be particularly true in the elderly population because of decreased acidity of the refluxed material or decreased pain perception. Many elderly patients have complications of GERD when they first present to a physician because they have had long-standing disease with minimal symptoms. For example, up to one third of patients with Barrett's esophagus are acid insensitive. In this group, adenocarcinoma may be the first and only manifestation of their reflux disease.

ENDOSCOPIC DIAGNOSIS OF ESOPHAGITIS

Endoscopy provides direct visualization of the esophageal mucosa and permits biopsies to be performed when needed. For simplicity it is reasonable to define esophagitis and complications of reflux disease with a grading scale from I to III. Overall, about 50% of patients with reflux shown by other studies have mucosal abnormalities endoscopically. However, endoscopic esophagitis has excellent specificity (approaching 95%) for GERD.5 In the absence of endoscopic evidence of GERD, microscopic lesions indicative of esophagitis may be present. Adequate, well-oriented esophageal biopsy specimens are essential for reliable histopathologic interpretation.

Grade I esophagitis. In the normal esophagus there is usually a pattern of fine, tiny, linearly arranged blood vessels that extend up to 3 cm above the gastroesophageal junction. Edema of the

esophageal mucosa causes loss of this fine vascular pattern and the squamocolumnar junction becomes indistinct. However, this occurrence and esophageal erythema are nonspecific findings of esophagitis, being present in up to 60% of healthy subjects. On the other hand, friability (i.e., bleeding in response to gentle contact with the endoscope) results because acid reflux induces mucosal thinning, which causes the capillary beds to come closer to the surface and the size of the vessels to increase. Friable areas may be associated with red streaks, which usually appear on the tops of the mucosal folds extending up from the squamocolumnar junction. These findings are less subject to observer variation and are the earliest signs of esophagitis.

Grade II esophagitis. Erosions represent thinning of the superficial epithelium and appear as whitish exudates surrounded by red halos of erythema. Erosions are typically contiguous with or appear just above the squamocolumnar junction. Single erosions are usually seen along the tops of the mucosal folds. As the disease becomes more severe, isolated erosions may coalesce and bridge adjacent folds.

Grade III esophagitis. The most severe damage to the esophagus produces ulcers that have some depth, a white or yellow base, and are variable in size and shape. Some ulcers are isolated; others circumferentially involve the squamocolumnar junction and are usually associated with stenosis of the esophageal lumen. Most patients with grade III esophagitis will have some complications of GERD, particular strictures, or Barrett's esophagus.

Complications of esophagitis. The lower esophageal ring (Schatzki's ring) is a diaphragm-like structure that results from mucosal hyperplasia of the squamocolumnar junction. Although it has been suggested that this is congenital, more recent studies confirm that it is a common complication of GERD. An esophageal stricture results when chronic ulcerative esophagitis progresses to panmural fibrosis.6 Peptic strictures, which typically involve the distal esophagus, are usually less than 1 cm long with a thickened, noncompliant, and shortened esophagus. In some patients severe esophagitis is complicated by a unique reparative process wherein the original squamous epithelium that lines the distal esophagus is replaced by metaplastic columnar epithelium, that is, Barrett's esophagus.' The new squamocolumnar junction is usually displaced proximally. Barrett's epithelium comprises three types of mucosa: specialized columnar epithelium that resembles intestinal mucosa, junctional-type epithelium, and gastric fundic-type epithelium. Specialized columnar epithelium is usually most proximal and is the only type with a malignant potential.

ROLE OF ENDOSCOPY VERSUS OTHER TESTS IN EVALUATING GERD

In most patients with classic symptoms of heartburn and regurgitation, the history is sufficiently typical to permit a trial of therapy without the need for diagnostic tests. Early investigation should be considered in the following cases: esophageal symptoms that do not respond to medical therapy, dysphagia, atypical manifestations of suspected GERD, manifestations that involve possible complications of GERD, or patients who are being considered for antireflux surgery.

Endoscopy. All patients who have persistent reflux symptoms or frequent relapses after H2 blocker therapy should undergo endoscopy at least once to identify the presence of esophagitis or

Barrett's esophagus and to exclude other upper gastrointestinal lesions that may mimic GERD. Symptoms are not a reliable predictor of esophagitis severity. Patients with erosive or ulcerative esophagitis will require long-term aggressive medical therapy and are more likely to experience complications of GERD. Patients with esophageal strictures and ulcerations identified by a barium esophagram should undergo endoscopy with biopsies to exclude associated malignancies. At that time, patients with peptic strictures may undergo therapeutic esophageal dilatations. Biopsies should be performed in patients diagnosed as having Barrett's esophagus to identify associated adenocarcinomas, which are found in I 0% of patients. Furthermore, these patients should be placed in a surveillance program because there is an increased risk of the development of adenocarcinoma over time.

Barium esophagram. A barium esophagram should be the first diagnostic procedure in most patients with dysphagia. If the patient has solid food dysphagia, the liquid component should be complemented with the administration of barium tablets, marshmallows, or solid food boluses to bring out subtle strictures and rings.8 The barium esophagram is an unreliable method for detecting reflux esophagitis because most cases include mild morphologic changes that are not perceptible on radiographs.

Prolonged esophageal pH monitoring. With use of a portable data logger and small pH electrode placed 5 cm above the LES, prolonged esophageal pH monitoring permits accurate quantification of acid reflux over 24 hours and accurate correlation of symptoms with acid reflux episodes. Prolonged esophageal pH monitoring, which is usually performed in the patient's home or work environment where symptoms are more common, is the best test for diagnosing GERD; it has a sensitivity of 85% and a specificity above 95%. The test is most useful in evaluating patients with atypical manifestations of GERD or patients who have persistent symptoms despite aggressive medical therapy and no evidence of esophagitis by endoscopy.

TREATMENT

The rationale for GERD therapy depends on careful definition of specific goals. In patients without esophagitis, the therapeutic long-term goal is simply to relieve their acid-related symptoms. On the other hand, the ultimate goals in patients with esophagitis are to relieve symptoms and heal esophagitis while attempting to prevent further complications.

Life-style modifications. The use of simple lifestyle changes are particularly helpful in patients who do not have esophagitis. These changes should include the following: avoidance of large meals, which increase gastric volume; weight loss; consumption of supper at least several hours before bedtime and not lying down after meals to prevent supine reflux; and elevation of the head of the bed by 6-inch blocks to improve nocturnal clearance of refluxed acid. Other dietary changes may include avoiding agents that are direct esophageal irritants (e.g., citrus juices, tomato-based products, and coffee) or those that adversely affect LES pressure (fatty foods, chocolate, and carminatives). Drugs that decrease LES pressure or impair esophageal motility and gastric emptying should be avoided if possible.

Antacids and alginic acids. Antacids and alginic acids may help relieve intermittent symptoms of heartburn or regurgitation. However, they are not effective in healing esophagitis.

Prokinetic drugs. Bethanechol and metoclopramide are prokinetic drugs that are effective in relieving heartburn symptoms, but their efficacy in treating esophagitis is equivocal. On the other hand, the new prokinetic drug cisapride may be more effective than placebo and equal to H2 antagonists in controlling reflux symptoms and healing milder grades of esophagitis.

H2 antagonists. Despite advertising to the contrary, all H2 antagonists are equally effective in relieving symptoms and healing esophagitis when used in proper doses, that is, cimetidine, 800 mg b.i.d.; ranitidine, 150 mg q.i.d.; famotidine, 20 mg b.i.d.; and nizatidine, 150 mg b.i.d. Clinical trials show that heartburn can be significantly decreased by H2 antagonists when compared with placebo, although symptoms are rarely abolished. Overall, esophagitis healing rates with H2 antagonists rarely exceeded 60% to 75%, even after 12 weeks of treatment.9 The most important factor in healing rates is the degree of esophagitis before therapy; grades I and II esophagitis heal in 75% to 90% of patients, whereas grades III and IV heal in only 40% to 50% of patients. Therefore H2 antagonists may be best for treating patients with milder grades of endoscopic esophagitis.

Omeprazole. Omeprazole is a potent and long acting inhibitor of both basal and stimulated gastric acid secretion. Studies show that omeprazole (20 to 40 mg every morning) completely abolishes reflux symptoms in most patients with severe GERD, usually within 1 to 2 weeks. Complete healing of even severe ulcerative esophagitis occurs after 8 weeks in more than 80% of patients. Comparison studies show that omeprazole is superior to H2 antagonists in relieving symptoms and healing esophagitis. Peptic strictures associated with esophagitis heal faster and require fewer dilatations when treated with omeprazole compared with H2 antagonists. Side effects with omeprazole are minimal; however, there is concern about long-term safety because this drug has caused carcinoid tumors in rats.

Antireflux surgery. Although we can virtually heal all cases of acute esophagitis, patients invariably will have a relapse within 1 year of discontinuation of therapy. H2 antagonists, cisapride, and omeprazole may be considered for long-term maintenance therapy. However, antireflux surgery is an important alternative and should be strongly considered in younger patients with severe esophagitis who otherwise would require lifetime medical therapy. Other indications include recurrent strictures that are difficult to dilate, non-healing ulcers, severe bleeding from esophagitis, and reflux related complications of the respiratory tract that do not respond to medical therapy. Careful assessment of esophageal function (manometry and pH testing) before surgery and a skilled, experienced surgeon are critical to the success of antireflux surgery. When these criteria are met, the results of antireflux operations, although not perfect, are generally good: up to 80% to 90% of patients have satisfactory long-term outcome.

Dyspepsia

Maj. Gavin S. Young, MC, FS

1) Introduction

The term dyspepsia is used frequently by patients and physicians alike, but a precise definition of dyspepsia is difficult to obtain. The term "indigestion" is a good colloquial definition of dyspepsia as it relates the combination of symptoms often related to food that includes epigastric pain or discomfort, bloating, belching and eructations, and flatulence. Many often include symptoms of nausea, early satiety, distension, and heartburn into this symptom complex as well (**Table 1**).

The consistent feature among dyspeptic patients is the clustering of symptoms in the upper abdomen, between the xiphoid process and the umbilicus. Symptoms referred to the lower abdomen (below the umbilicus) are usually not a manifestation of dyspeptic problems but may indicate a lower intestinal problem. Symptoms can be persistent or recurrent and patients may present to the physician soon after the onset of symptoms or wait a considerable time before seeking medical help.

The main goal of medical evaluation of dyspeptic patients is to distinguish between organic processes (peptic ulcer disease, chronic pancreatitis, gastroesophageal reflux disease or esophagitis, cholelithiasis, etc.) and functional dyspepsia The organic entities will be discussed throughout this symposium so the remainder of this discussion will focus on the condition known as *functional dyspepsia* or *Non-Ulcer Dyspepsia (NUD).*

Dyspepsia is a common problem in the primary care setting as well as in gastroenterology referral centers. It affects 25 to 30% of the community at some time in their lives with a prevalence ranging from 2.5% to 41% [1]. Due to the high prevalence of dyspepsia, much attention and resources are devoted in the evaluation and treatment of this disorder, especially with the abundant technological advances that have been made in the digestive diseases in the past few decades. However, as health care transitions into a period of constrained financial resources, a better understanding of the diagnostic approach and therapy of dyspepsia is needed at both the primary care and subspecialty levels of medicine.

2) Pathophysiology

To date, there is no unifying theory on the cause of dyspepsia and the pathophysiologic mechanisms that generate dyspepsia are imperfectly understood. Many different mechanisms may contribute to the complex of symptoms in dyspeptic patients and a variety of therapies have been tried aimed at treating these different mechanisms. However, no single therapy has been shown to be the panacea for all dyspeptic patients.

The main categories of pathophysiologic mechanisms felt to be associated with dyspepsia are outlined in **Table 2**. However, these diverse proposed mechanisms of disease raises the question: Is dyspepsia a single entity or multiple syndromes? The broad concept of functional dyspepsia has several disadvantages since it is vague and covers too many patients and it does not relate specific physiologic abnormalities to specific symptoms. This broad concept of a

single entity makes it difficult to evaluate the efficacy of various therapies on such a heterogeneous group of patients. Thus, attempts have been made to subclassify dyspepsia into three main categories based on the type of symptoms that predominate in a given patient: **1) Reflux-Like Dyspepsia; 2) Ulcer-like Dyspepsia; and 3) Dysmotility-like Dyspepsia** [2].

TABLE 1

Symptoms of Dyspepsia
Upper Abdominal Pain or Discomfort
Bloating
Belching / Eructations / Flatulence
Nausea
Early Satiety
Heartburn

TABLE 2

Pathophysiologic Mechanisms
Gastric Acid Secretion
Helicobacter pylori
Abnormal Gastroduodenal Motility
Dietary Factors & Medications
Psychologic Factors

Reflux-Like Dyspepsia incorporates patients with predominantly heartburn and regurgitation symptoms in association with other typical dyspeptic symptoms. GERD probably does play a significant role in these patients since they are more likely to respond to therapies targeted at acid reduction. It is difficult clinically to fully differentiate between patients with reflux-like dyspepsia and those with GERD with negative or minimal lesions on imaging studies or endoscopy.

Ulcer-like Dyspepsia has epigastric pain that is often relieved by food or antacids as the hallmark symptom. Some of these patients may truly incorporate elements of acid related disease but response rates as a whole to acid reducing therapies is low and the evidence for acid hypersecretion in this subgroup is not convincing [3]. There is evidence for normal basal and stimulated acid output in several small studies of this patient population. In one study, patients with documented acid hypersecretion and dyspepsia underwent vagotomy. Despite a reduction in acid production as expected, many patients remained symptomatic [4]. In a recent study, esophagitis was found in about 50% of patients with ulcer-like dyspepsia suggesting that GERD may be a significant underlying problem in this subgroup of patients [5].

Dysmotility-like Dyspepsia is characterized more by complaints of early satiety, bloating or epigastric fullness, and nausea. These symptoms are thought to relate to abnormalities of gastric emptying or abnormalities of intestinal or gastroduodenal motility. Symptoms are usually worse postprandially and are often associated with symptoms of the Irritable Bowel Syndrome.

Despite attempts to subclassify patients, it is not easy to categorize a given patient into one or the other subgroups due to the significant overlap of symptoms in individual patients. Thus, whether one considers dyspepsia as a single entity or attempts to categorize it in subgroups, the nebulous nature of dyspepsia continues to thwart efforts at classification and continues to frustrate both patient and physician.

Gastric Acid Secretion: As mentioned above, most studies have failed to show a significant abnormality of gastric secretion in either the basal or stimulated state. Responses to Histamine-2 receptor antagonists (H2RA) in patients with ulcer-like and dysmotility-like dyspepsia have been

unconvincing. A meta-analysis of medical therapy in dyspepsia showed that pro-motility agents were superior to H2RA's and Placebo in decreasing dyspeptic symptoms [6].

Helicobacter pylori: Certainly the most recent hypothesis is that a significant amount of dyspeptic symptoms are caused by H. Pylori (HP) infection either due to the associated inflammation associated with infection or due to HP induced abnormalities of gastric motility. Unfortunately, studies evaluating the association of HP with dyspepsia and the response to HP eradication have yielded mixed results and many of these studies have methodological flaws. To date, there is no strong evidence that eradicating HP in patients with functional dyspepsia provides any long term relief. Research in the association of HP and dyspepsia has focused in three main areas: 1) Epidemiologic associations; 2) Pathophysiologic associations; and 3) Eradication studies.

Approximately 50-60% of patients presenting with dyspepsia will have evidence for HP infection, though the prevalence varies with the socioeconomic environment being studied. However, in four HP prevalence studies in dyspepsia, only two showed a statistically higher prevalence of HP in dyspeptics vs. controls [7]. A recent meta-analysis of seroprevalent studies in dyspeptic patients concluded that the relative risk of non-ulcer dyspepsia was 2.3 (95% CI 1.9-2.7) in HP infected cases, irrespective of study quality and background prevalence of HP infection [8]. However, this analysis included studies that had large age and socioeconomic discrepancies between the dyspeptic population and asymptomatic controls.

Acute infection with HP results in an acute gastritis associated with symptoms of upper abdominal pain, nausea, vomiting, and fullness. Symptoms usually occur within the first week of infection in 60% and resolve within 1 to 2 weeks. Chronic HP infection is characterized by a chronic active gastritis. However, there is no documented evidence that chronic dyspepsia develops as a consequence of the transition from acute to chronic histologic gastritis. Chronic HP infection is also associated with the release of numerous chemokines and cytokines but there are no definitive studies linking these HP related phenomena to the symptoms of dyspepsia. Could there be a subgroup of symptoms that can be linked to HP? Unfortunately, there is no definite symptom complex that can be linked to HP. Numerous studies have identified individual symptoms that may be more prevalent in HP infected patients but unfortunately there is no concordance among those studies (belching, bloating, epigastric pain/burning have all been individually identified in different studies) and other studies have found no association of HP and individual symptoms in patients with functional dyspepsia. Although there is no abnormality of acid secretion in dyspeptic patients, El-Omar et al. found that a subgroup of patients with dyspepsia and HP infection had higher stimulated gastric acid output, though lower than seen in duodenal ulcer patients [9]. However, asymptomatic HP infected controls may have a similar abnormality and confirmatory studies with HP negative dyspeptic controls are lacking. Abnormalities of gastric motility and sensation have been suggested as a potential cause of dyspepsia (see below). Most studies have reported no association of HP with abnormal gastric motor function in non-ulcer dyspepsia and those that do offer conflicting, confusing results.

Eradication studies have yielded even more conflicting results. Many of the studies are of flawed study design or are too small to yield significant power in their analysis. In a review of available studies, Talley identified 8 trials that suggested a benefit of therapy and 8 that didn't [10]. Laheij et al. reviewed 10 studies of various design (7 blinded, 6 randomized, 3 both) and concluded that symptoms of non-ulcer dyspepsia improved in 73% of patients cured of HP compared with only 45% with persistent infection [11]. In a recent randomized, double-blind,

placebo controlled trial, Van Zanten et al. showed that there was no difference in symptomatic improvement in both the treated and control groups and that no overall difference was found between the groups at both 6 weeks and 6 months post-treatment [12].

Unlike the strong evidence linking HP with peptic ulcer disease, definite evidence of a link between HP and functional dyspepsia is still lacking with conflicting results reported in the literature. Although there may be a subgroup of patients with dyspepsia that could potentially benefit from HP eradication, larger, well designed and well-conducted studies are needed.

Gastroduodenal Motility Abnormalities: Delayed gastric emptying is reported in about 30% to 80% of patients with functional dyspepsia [13]. Abnormalities of solid food emptying are more common than liquid emptying, but this is an inconsistent finding. However, despite this relatively common finding among dyspeptic patients, there is poor correlation between gastric emptying and symptoms and they may vary independently in response to therapy [14]. Antral hypomotility has also been reported in 25% to 70% of dyspeptic patients and have been associated with decreased vagal tone, suggesting that extrinsic nerve dysfunction may affect antral contractility and symptoms in these patients [15].

Duodenogastric reflux of bilious duodenal content with subsequent gastric irritation has been proposed as a possible etiology for dyspepsia. However, in a well designed study, duodenogastric reflux was not increased in patients with functional dyspepsia and does not appear to be a significant etiologic factor in the pathogenesis of dyspepsia.

Diet and Drugs: Certain lifestyle choices may predispose to a greater amount of dyspeptic symptoms. Tobacco, alcohol, carbonated beverages, caffeine containing foods, etc all may predispose to increases in gastric acid production and gastroesophageal reflux. Drugs that can cause dyspeptic symptoms without overt mucosal damage include NSAIDS, antibiotics, digitalis, theophylline, etc. Although there is a paucity of scientific data regarding some of these correlations with symptoms, common sense and experience are important in this regard.

Psychological Factors: Social factors have been associated with dyspepsia to include: 1) advancing age, male gender, unmarried status, and social class incongruity [16]. Other studies have found a correlation between symptoms and adverse life events in patients with dyspepsia. In studies using the MMPI, most patients with functional dyspepsia score higher than healthy controls in measures of anxiety, neuroticism, depression, and hypochondriasis [17]. However, these same traits can be found in patients with other digestive problems as well (PUD, biliary tract disease, IBS, etc). Many studies conclude that a high level of anxiety and neuroticism are common in patients with dyspepsia.

3) Diagnosis

As stated previously, the challenge to the physician when presented with a dyspeptic patient is to differentiate organic disease from functional dyspepsia. In clinical practice, this may be a difficult task given the non-specific and overlapping nature of many upper gastrointestinal problems. **Table 3** contains many of the disorders commonly associated with dyspepsia.

TABLE 3

Alimentary Tract	Metabolic	Other
Peptic Ulcer	Diabetes mellitus	Cardiac disease / Ischemia
GERD	Thyroid disease	Mesenteric Ischemia
Gastritis / Duodenitis	Hyperparathyroidism	Collagen Vascular Disease
Biliary Tract Disease	Electrolyte abnormalities	Giardiasis / Strongyloides
Acute / Chronic Pancreatitis		Lactose Intolerance
GI Neoplasia (Cancer)		Celiac Sprue
Malabsorption Syndromes		
Gastric Infiltrations		

Given such a laundry list of disorders with overlapping presentations, it isn't surprising that even experienced clinicians only reach a diagnostic accuracy of 50% [7]. Although various scoring systems and questionnaires have been developed to improve diagnostic accuracy, they are predominantly research tools and are not useful in a busy clinical practice. Thus, as clinicians, we must rely on our history and physical skills to evaluate patients for signs and symptoms of serious organic disease.

A history of gastrointestinal bleeding, abnormal weight loss, persistent vomiting, dysphagia or odynophagia, or new onset symptoms in a patient over the age of 45 should prompt an immediate evaluation. A thorough evaluation of cardiac risk factors should always be sought for and if present, consideration should be given for a potential cardiac problem. The history should ascertain which symptom cluster the patient has since this will help guide the initial evaluation. A complete drug history is important and NSAIDS should be discontinued whenever possible.

Physical examination findings of an abdominal mass, jaundice, bloody stools, lymphadenopathy, organomegaly, ascites, or moderate to severe epigastric tenderness are also signs of potential organic disease and should be promptly evaluated. Musculoskeletal problems should be sought for since many times costochondritis or rib-tip syndromes will be related by the patient in terms of vague upper abdominal pain.

Initial laboratory analysis should be focused and based on the history and physical findings. Initial investigations might include a CBC, ESR, LFT's, and FOBT. If pancreaticobiliary disease is strongly suggested, an abdominal ultrasound should be obtained.

Despite the best history and physical examination, it is still difficult to confirm or exclude the presence of significant organic disease. Indeed, since cancer is the most dreaded diagnosis that patients want to avoid (and physicians don't want to miss), many patients and physicians alike prefer to have some form of structural evaluation (endoscopy, UGI series, etc.) to put their fears at rest. In pooled endoscopic data from the United Kingdom in 3,667 dyspeptic patients, cancer was found in 2.0% (**Table 4**). However, it has been shown that cancer rarely presents as dyspepsia in patients under the age of 55 without some sinister signs or symptoms [18]. Thus, in an era of cost containment, use of more expensive and invasive diagnostic tools should be reserved for patients in whom significant disease is strongly suspected. For patients under the age of 50 without "red flag" signs or symptoms, empiric therapy can be safely instituted and endoscopy or barium studies reserved for treatment failures or relapses. This then begs the question: Which empiric therapy should be given?

TABLE 4 Endoscopic Diagnosis in 3,667 Dyspeptic Patients

Normal	Reflux	Duodenitis, Gastritis	Ulcer	Cancer
1232 (33.6%)	878 (23.9%)	765 (20.9%)	729 (19.9%)	74 (2.0%)

There has been much debate over whether HP should be sought for as part of the initial evaluation in dyspeptic patients. Proponents of this approach argue that it is cost effective and avoids unnecessary endoscopies without putting patients at a significant disadvantage. A prospective study by Patel et al. showed that serologic screening of dyspeptic patients for HP under the age of 45 together with a history of "red flag" symptoms and NSAID use avoided unnecessary endoscopies [19]. However, a theoretical decision analysis by Silverstein et al. showed only a 2.5% ($53.24) cost advantage over a one year time frame for the empirical HP therapy strategy (noninvasive HP testing with subsequent eradication therapy without confirmatory endoscopy for HP+ patients) over the initial endoscopy strategy [20]. There was no significant difference in life expectancy after diagnosis between the different study arms (23.49 yrs for initial endoscopy vs 23.48 yrs for an initial empiric therapy). In another cost benefit analysis of the "test and treat" approach to HP and dyspepsia, Sonnenberg showed that a response to HP eradication in 5-10% of all patients with nonulcer dyspepsia would make screening and treatment for H. pylori a beneficial option, irrespective of any other potential benefits. If ulcer prevention were associated with long term benefit of $4000 or more and if the ulcer prevalence rate exceeded 10% of all dyspeptic patients, serological screening for H. pylori would also pay off [21]. However, the authors could not recommend treating all dyspeptics who test positive for HP until there is unequivocal evidence of a significant response to HP eradication in non-ulcer dyspepsia. Despite these studies showing marginal to no benefit of the test and treat strategy, other analytic models have reported a significant cost savings. Ofman et. al. showed that in a decision analysis comparing the costs and outcomes of initial anti-HP therapy and initial endoscopy favored empiric therapy by a margin of $456 per patient treated [22]. Similarly, Vakil and Puetz recently reported in abstract form the one year outcome of a test and treat strategy in HP infected dyspeptic patients [23]. Their results in 93 patients showed that at one year, complete symptomatic cures were significantly greater in infected patients who had HP eradicated (76%) than in patients without HP eradication (36%, p=0.05). However, only 28 of 93 (30%) had evidence of active HP infection and only the results in the HP infected population are offered, leaving us to speculate whether there was any significant difference between uninfected dyspsptics and those who underwent successful eradication.

Cost analysis studies offer a somewhat rigid statistical evaluation due to the limitations that are necessary to perform such an analysis. Other factors such as quality of life, patient satisfaction, etc. are not addressed in these statistical analyses and in reality may have significant impact on these studies final conclusions. In an attempt to address patient satisfaction, a recent analysis of patient preference indicated that 50% of patients would prefer to undergo initial endoscopy to put their fears of significant organic disease to rest as opposed to the test and treat pathway. Unfortunately, until large, prospective, randomized studies are performed, we will need to rely on the information these cost analysis studies offer us and put them in perspective with our particular medical environment and patient preferences.

4) Treatment

Empiric therapy with anti-secretory of prokinetic agents is warranted in patients under the age of 45 - 50 as long as there are no sinister history or physical findings. The initial class of drug chosen depends on the clinician's suspicions of whether an acid-predominant or motility-predominant component is present. For patients with reflux-like dyspepsia, initial therapy with the least expensive H2RA would be reasonable given the similar efficacy rates among the various H2RA's. However, the results with H2RA's reported in the literature are conflicting with about half the studies reporting no effect; whereas, some of the larger studies show statistical advantages over placebo. For patients with dysmotility-like or ulcer-like dyspepsia, empiric trials of a prokinetic agent like cisapride would be a reasonable starting point as there is some evidence that prokinetic agents are superior to H2RA's in these groups of patients [6]. Use of metoclopramide should be limited due to its adverse CNS side effects. Other prokinetic agents like domperidone await FDA approval but are available on a compassionate use basis.

For patients failing empiric therapy, a more detailed diagnostic investigation should be initiated. Referral to a gastroenterologist for endoscopy or to a radiologist for contrast barium studies is warranted. Additional special testing such as CT, MRI, nuclear medicine motility studies, etc. are usually not needed and their use should be individualized to the situation and patient.

Conclusion

Dyspepsia is not a unique medical condition but rather a symptom complex that may herald significant organic disease or be a manifestation of a more functional problem. Although there are many hypotheses regarding the pathophysiology of dyspepsia, there is no unifying abnormality that has been identified to date. Attempts to definitively link Helicobacter pylori with non-ulcer dyspepsia have been mixed and there is no definitive evidence that such a relation exists at present time. Cost effective studies regarding the "test and treat" hypothesis for HP in dyspeptic patients have shown marginal cost benefits and rely on the response rate of nonulcer dyspepsia to H. pylori eradication and secondly by the monetary benefit of ulcer prevention and the prevalence rate of peptic ulcer in H. pylori-positive patients. Empiric therapy for patients under the age of 50 and forgoing expensive diagnostic testing is warranted when there are no "red flags" that suggest the presence of significant organic disease, and treatment should seek to alleviate symptoms without prolonged therapies of uncertain effectiveness.

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Peptic Ulcer Disease & H. pylori

Maj. Gavin S. Young, MC, FS

1) Introduction

The approach to peptic ulcer disease (PUD) has been revolutionized in the past few decades with the advent of progressively more potent anti-secretory therapy. However, the most significant discovery has been that of *Helicobacter pylori* (HP) and its association with PUD. It is now accepted that the majority of gastric and duodenal ulcers are related to infection with HP and that the recurrent nature of the "disease" can be "cured" with eradication of HP. Nonsteroidal anti-inflammatory drugs (NSAIDS) continue to proliferate and represent the other major independent cause of a significant number of peptic ulcers. NSAIDS are responsible for the large majority of PUD complications and despite the explosion of NSAIDS on the market, there are still few effective strategies for preventing these significant complications.

2) PUD Epidemiology and Economics

In the United States, there are 350,000 to 500,000 new ulcer cases and more than one million ulcer-related hospitalizations each year. The direct costs to the health care system are more than $2 billion per year and indirect costs (lost productivity, time from work, etc.) exceed more than $500 million.

The estimated lifetime prevalence of PUD in the United States is approximately 10% with the incidence of duodenal ulcers (DU) (0.06% - 0.3% per year) being greater than gastric ulcers (GU) (about 0.03% per year). However, in the past few decades, there have been significant changes in the epidemiology of PUD. Hospitalization rates for uncomplicated DU is decreasing while GU and complicated PUD rates have increased. The male predominance of PUD is shifting to a gender neutral position and PUD is becoming less of a disease in the young and more significant in the elderly.

3) Etiologic Factors

Many of the traditional theories on the contributing factors to the development of PUD are no longer valid. Diet, alcohol, stress, blood type, etc. are no longer felt to be significantly related to the development of PUD. Tobacco use is still felt to contribute, but its role is questionable following HP eradication. Today, HP and NSAIDS are felt to be the main etiologic factors in the pathogenesis of PUD. Unfortunately, a survey conducted in 1995 shows that nearly 90% of Americans with digestive disorders still believe that stress causes ulcers and 60% think poor diets cause ulcers as well. More than 90% of these patients were totally unaware of HP and its association with PUD.

4) History and Epidemiology of HP

Human gastric bacteria were first discovered in the early 1900's but were dismissed as contaminants in the 1950's. Interest recurred in the 1970s and in 1982, Marshall successfully cultured the organism and named it *Campylobactor pyloridis*. In 1989*Campylobactor pyloridis* was reclassified as *Helicobacter pylori.* Studies showing the reduction in ulcer recurrence as a result of HP eradication were available as early as 1987, but it wasn't until 1994 that the NIH consensus panel issued guidelines for the management of ulcer disease, taking HP into account.

Humans serve as the natural host of infection, and although there is evidence supporting both fecal-oral and oral-oral spread, the exact mechanism by which transmission occurs remains unclear. Humans appear to be the only reservoir for H pylori infection. Although the major mode of transmission of H pylori infection is not known, available information supports spread by human contact. Iatrogenic spread through contaminated gastrointestinal equipment has been documented. As with other iatrogenically spread infections, this source can be eliminated by following proper equipment cleaning procedures and universal precautions.

HP is felt to colonize 50-60% of the world's population. The infection is typically acquired in childhood with studies showing serologic evidence of infection in children 6 months of age after the disappearance of maternal antibodies. There is a significant inverse association with socioeconomic status with seroprevalence in the general population with some third world countries as high as 70 - 80%. HP prevalence in developed countries is different with infection in childhood being less common but increasing with age at a rate of ~3% per decade.

5) HP and GI Disease Associations

HP is associated with a number of common upper GI disorders. Nearly 100% of patients with active chronic gastritis have associated HP infection. As stated above, >90% of DU's and 60-90% of GU's are associated with HP infection. Nonulcer dyspepsia (NUD) is a very common problem with a variety of different causes. Although infection with HP in NUD is found in 35 - 60%, the relationship of NUD to HP is not as well established as it is in PUD. Although no studies have currently proven a direct cause and effect relationship, gastric cancer is felt to be associated with HP due to the epidemiologic and demographic similarities of the two diseases. Rates of prevalence of HP seropositivity correlate closely with the incidence of gastric cancer in any given population. Gastric cancer has been shown to be more common in people in patients chronically infected with HP compared to those who weren't infected with an attributable risk of 46% - 63%. Low grade B-cell non-Hodgkins lymphomas of the MALT (mucosa associated lymphoid tissue) type have been associated with HP infection. In one study, >90% of MALT lymphomas had associated HP infection and regression of the lymphoma has been shown with HP eradication therapy alone.

6) Pathogenesis of HP in PUD

HP only infects gastric mucosa since only gastric-type mucosa has the specific adherence receptors recognized by the organism. Thus, how can a bacterium that lives in the stomach result in ulcers in the duodenum and why are there HP infected individuals who never develop ulcers?

HP infection results in elevated gastrin levels as a result of impaired somatostatin-mediated inhibitory control. The degree of subsequent acid production is variable and depends on a given individual's sensitivity to gastrin mediated acid production (host factor). DU patients have been shown to be acid hypersecretors in response to gastrin irrespective of HP status.

Hypersecretion of acid results in irritation and subsequent gastric metaplasia in the duodenal bulb; thus, presenting HP with an opportunity to infect those areas in the duodenum. Certain HP strains (CagA positive) incite a greater inflammatory response and lead to mucosal damage (virulence factor) that can result in frank ulceration. Therefore, the current hypothesis is that HP infection in genetically predisposed individuals results in PUD due to the combination of certain host and virulence factors.

7) Diagnosis of PUD and HP

The symptoms of peptic ulcers include epigastric pain or burning that can also be described as gnawing or hunger-like. The pain typically occurs 1 to 3 hours after meals and can be relieved with food or antacids. Symptoms can occur at night and awake patients from sleep. Symptoms of PUD are typically recurrent with clustering over time. Unfortunately, "classic" presentations of PUD only occur about 20% of the time and the symptoms described here are nonspecific and differentiate poorly between DU, GU, and NUD. Thus, absolute diagnosis of PUD relies on visualization of the ulcer either by UGI series or upper endoscopy.

Diagnostic tests for HP can be divided into invasive and noninvasive tests. Invasive tests are obtained at the time of upper endoscopy and noninvasive tests are now readily available in the primary care setting. The various tests and approximate costs are outlined below:

Test	Sensitivity	Specificity	Estimated Cost
Noninvasive			
Serology			
--Office	90%	90%	$15
--Lab	90%	92%	$65
Urea Breath Test	90%	96%	$200
Invasive			
Rapid Urease Test	90%	98%	$10
Histology	93%	99%	$150
Culture	80%	100%	$150

Thus, balancing diagnostic accuracy with cost, the best noninvasive test for the initial diagnosis of HP infection is a serology and the best invasive test (when endoscopy is required) is a rapid urease test (RUT). However, HP antibodies persist after eradication and are thus a poor test to evaluate a patient for continued or recurrent infection following therapy. Documentation of eradication is important in patients with complicated PUD but **not** necessary in patients with uncomplicated disease. In those patients where documentation of eradication is required and follow up endoscopy is not needed, the urea breath test (UBT) is the most accurate and cost effective strategy. If repeat endoscopy is required, then RUT is the preferred method of evaluation.

The real question is: Who should we test for HP? The European Helicobacter Study Group and other international representatives have published recommendations for HP eradication (thus inferring HP testing) based on available medical evidence. **Strongly recommended indications** with unequivocal evidence include: active PUD, history of PUD, complicated PUD, and MALT lymphoma; those with supportive evidence include gastritis with severe abnormalities, and following early resection for gastric cancer. **Advisable indications** with equivocal evidence include NUD (after full investigation), strong family history of gastric cancer, planned or existing NSAID therapy, and patient desire for eradication; those with supportive evidence include long-term PPI therapy (though the data for this recommendation has been subsequently discredited) and following surgery for PUD. **Uncertain indications** with equivocal evidence include extra-alimentary tract disease, asymptomatic individuals, and to prevent gastric cancer in the absence of risk factors.

Much debate has been given to the "test and treat" strategy for patients presenting with dyspeptic symptoms. Although the actual prevalence of PUD in a group of dyspeptic patients is low, proponents of this approach argue that it is cost effective and avoids unnecessary diagnostic

tests in the subgroup of patients under the age of 50 who have no "red flag" symptoms or signs (wt. loss, bleeding, early satiety, etc.). A prospective study by Patel et al. showed that serologic screening of dyspeptic patients for HP under the age of 45 together with a history of "red flag" symptoms and NSAID use avoided unnecessary endoscopies. However, a theoretical decision analysis by Silverstein et al. showed only a 2.5% ($53.24) cost advantage over a one year time frame for the empirical HP therapy strategy (noninvasive HP testing with subsequent eradication therapy without confirmatory endoscopy for HP+ patients) over the initial endoscopy strategy. There was no significant difference in life expectancy after diagnosis between the different study arms (23.49 yrs for initial endoscopy vs 23.48 yrs for initial empirical therapy). In another cost benefit analysis of the "test and treat" approach to HP and dyspepsia, Sonnenberg showed that a response to HP eradication in 5-10% of all patients with nonulcer dyspepsia would make screening and treatment for H. pylori a beneficial option, irrespective of any other potential benefits. If ulcer prevention were associated with long term benefit of $4000 or more and if the ulcer prevalence rate exceeded 10% of all dyspeptic patients, serological screening for H. pylori would also pay off. However, the authors could not recommend treating all dyspeptics who test positive for HP until there is unequivocal evidence of a significant response to HP eradication in non-ulcer dyspepsia.

Despite these studies showing marginal to no benefit of the test and treat strategy, other analytic models have reported a significant cost savings. Ofman et. al. showed that in a decision analysis comparing the costs and outcomes of initial anti-HP therapy and initial endoscopy favored empirical therapy by a margin of $456 per patient treated. Similarly, Vakil and Peutz recently reported in abstract form the one year outcome of a test and treat strategy in HP infected dyspeptic patients. Their results in 93 patients showed that at one year, complete symptomatic cures were significantly greater in infected patients who had HP eradicated (76%) than in patients without HP eradication (36%, p=0.05). However, only 28 of 93 (30%) had evidence of active HP infection and only the results in the HP infected population is offered, leaving us to speculate whether there was any significant difference between uninfected dyspeptics and those who underwent successful eradication.

Cost analysis studies offer a somewhat rigid statistical evaluation due to the limitations that are necessary to perform such an analysis. Other factors such as quality of life, patient satisfaction, etc. are not addressed in these statistical analyses and in reality may have significant impact on these studies final conclusions. In an attempt to address patient satisfaction, a recent analysis of patient preference indicated that 50% of patients would prefer to undergo initial endoscopy to put their fears of significant organic disease to rest as opposed to the test and treat pathway. Unfortunately, until large, prospective, randomized studies are performed, we will need to rely on the information these cost analysis studies offer us and put them in perspective with our particular medical environment and patient preferences.

8) Therapy of PUD and HP

In general, the clinician has three major goals when faced with a patient with ulcer disease: relieve symptoms, heal the ulcer, and prevent recurrence. Acid suppression usually relieves symptoms and heals the ulcer while eliminating NSAIDs and eradicating HP now prevent recurrence. Thus, the approach to treating patients with PUD depends on whether they are taking NSAIDS, are infected with HP, or both. In patients with ulcers, NSAIDs should be discontinued and HP infection must be sought for since it has been shown that treating the HP infection heals ulcers faster and independent of the use of antisecretory therapy. However, the main advantage

of treating HP in patients with PUD is not to heal ulcers faster, but to dramatically reduce the subsequent recurrence of ulcers. Numerous studies have shown remarkable reductions in the 1 and 2 year recurrence rates. The 68 - 86% one year and 91% two year PUD recurrence rates can be reduced to 1-8% recurrence with successful HP eradication.

Traditional therapy of PUD with antisecretory therapy has centered around the use of H-2 receptor antagonists (H2RA's). Despite advertising claims, 8 week healing rates in DU is equivalent among all the H2RA's and similar to the 4 week healing rates seen with proton pump inhibitors (PPI's). Sucralfate's 8 week healing rates for DU are similar to those seen with H2RA's. Although there are small differences between these therapies, they are of minimal clinical difference and cost, patient tolerance, and compliance have become the important factors discriminating alternative therapies. Healing doses of antisecretory therapy are:

Drug	Regimen	4 week healing	8 week healing
H2RA			
Cimetidine	800 mg QHS	Equivalent for all	Equivalent for all
Ranitidine	300 mg QHS	H2RA's	H2RA's
Famotidine	40 mg QHS	80%	90%
Nizatidine	300 mg QHS		
PPI's			
Omeprazole	20 mg QAM	85%	95%
Lanzoprazole	15 mg QAM	85%	95%
Others			
Sucralfate	1 gm QID	75%	86%
Antacids	Lots!	75%	--

There are numerous HP therapies reported in the literature using various combinations of antisecretory medications and antibiotics for variable durations. In the United States, the FDA has recently approved a number of regimens with eradication efficacies ranging from 70% to 90%. Many factors influence the efficacy of a particular regimen. Patient compliance and tolerance as well as bacterial resistance are the main factors in efficacy. Single agent therapies are ineffective, induce microbial resistance at an accelerated rate, and should be avoided.

FDA approved HP treatment regimens (listed in order of FDA approval):

1) **OC**--Omeprazole 40 mg QD + clarithromycin 500 mg TID for 2 weeks, then Omeprazole 20 mg QD for an additional 2 weeks.
2) **RBC-C**--Ranitidine Bismuth Citrate (RBC) 400 mg BID + clarithromycin 500 mg TID for 2 weeks, then RBC 400 mg BID for an additional 2 weeks
3) **BMT**--Pepto-Bismol 525 mg QID + metronidazole 250 mg QID + tetracycline 500 mg QID for 2 weeks + H2RA therapy as directed for 4 weeks.
4) **OAC**--Omeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID for 2 weeks (May substitute lansoprazole 30 mg for omeprazole 20 mg)
5) **MOC**-- Omeprazole 20 mg BID + metronidazole 500 mg BID + clarithromycin 500 mg BID for 2 weeks (May substitute lansoprazole 30 mg for omeprazole 20 mg)
6) **RAC**--RBC 400 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID for 2 weeks
7) **RMC**--RBC 400 mg BID + metronidazole 500 mg BID + clarithromycin 500 mg BID for 2 weeks

Cost effective analyses of different HP therapies have shown BMT to be the most cost effective strategy ***if*** metronidazole resistance is < 36% and compliance is > 53%. Unfortunately, in actual practice, we rarely know the drug resistance patterns of HP in our community. To address this, Vakil and Fennerty studied the cost effectiveness of various strains using data variables from the Portland, Oregon area. Their results showed that MOC was the most cost effective strategy and that cost effectiveness of HP eradication was a function of *therapeutic efficacy* and not *initial drug costs.*

Most of the data on maintenance therapy was published in the pre-HP era. Eradication of HP has recurrence rates lower than that of traditional maintenance strategies (about 5-10% vs 15-20%). As a consequence, maintenance therapy in uncomplicated ulcer disease in which HP has been eradicated is unwarranted. The 1994 NIH consensus statement supported the use of maintenance therapy in patients with complicated ulcer disease (bleeding, perforation, obstruction) regardless of HP eradication. Since then, there have been several small studies showing that there was no significant adverse outcome in patients with bleeding ulcers who were not put on maintenance therapy following HP eradication. However, the duration of follow up in these studies is short (1 to 2 years) and the magnitude of the reduction remains to be firmly established. Therefore, maintenance therapy with nocturnal half-therapeutic doses of H2RA's should still be offered according to the NIH consensus conference in patients with complicated PUD. This has proven effective in reducing recurrences for up to 5 years. The efficacy of continuing maintenance therapy beyond 5 years is unknown and left to the discretion of the physician.

9) PUD and NSAIDs

More than 1% of the US population are daily NSAID users and more than 70 million prescriptions for NSAIDs are filled yearly. NSAIDs are ubiquitous since they are contained in over 200 over-the-counter products and patients may not even be aware they are consuming them. Dyspeptic symptoms occur in 10 - 15% of patients taking frequent NSAIDs and with chronic use, ulcers develop in about 30%. Unfortunately, there is a poor correlation between dyspeptic symptoms and the presence of overt ulceration. Thus the best way to avoid NSAID damage is to avoid NSAIDs or use the lowest possible dose in those who absolutely require them.

Since a significant proportion of PUD complications are attributable to NSAIDs, prophylactic strategies have been developed. However, not everyone taking NSAIDs require prophylaxis since the overall incidence of significant GI complications is small. Patients who are considered to be at high risk for NSAID ulcers and complications are: 1) patients over the age of 60, 2) Significant comorbid diseases (cardiovascular disease, severe COPD, renal disease, cirrhosis, etc.), 3) previous history of PUD or a PUD complication, 4) High dose or multiple NSAIDs, and 5) concomitant therapy with corticosteroids. Prophylaxis should only be considered in high risk patients.

H2RAs have been shown to reduce the incidence of NSAID related DU's but not GU's. At present, the only FDA approved medication for NSAID prophylaxis is misoprostol. In a large, randomized, blinded, placebo controlled trial, misoprostol significantly reduced gastroduodenal ulceration from 11.5% to 2.8%. This significant reduction was seen for both DU's and GU's. However, a serious criticism of this study was that it did not determine the reduction of NSAID related clinical *complications*, which after all is what we are trying to avoid. The MUCOSA trial subsequently enrolled almost 9,000 patients and randomized them to misoprostol 200mcg QID or

placebo and PUD complications (perforation, bleeding, obstruction) were measured as clinical outcomes. The authors reported an overall 40% reduction in complications in the misoprostol group compared with placebo (0.95% overall complication rate in placebo group, 0.57% overall complication rate in treatment group: p=0.049). However, if one looks at the specific complications, only perforation and obstruction were significantly reduced and no difference in bleeding complications were seen. There was also a significantly greater amount of patients who withdrew from the misoprostol group due to adverse side effects ($p < 0.001$). Thus, misoprostol reduces but does not prevent gastroduodenal ulceration and the reduction in clinical complications may not be as significant as the literature suggests.

PPI's have been studied as alternatives to misoprostol in the prevention of NSAID gastroduodenal injury. Preliminary data from Europe shows that omeprazole reduced gastroduodenal injury due to NSAIDs.

The ASTRONAUT and OMNIUM trials have compared omeprazole with H2RAs, misoprostol, and placebo. Preliminary results show that in 425 patients with healed NSAID ulcers, omeprazole 20 mg QD maintained remission for 6 months in 72% compared to 59% on ranitidine 150 BID (p=0.004). In 725 patients with healed NSAID ulcers, omeprazole 20 mg QD maintained remission for 6 months in 61% compared to 48% for patients on misoprostol 200 mcg BID and 27% for placebo treated patients (p=0.001 & p=0.0001 Miso & Plac vs Omep respectively). Patient drop out due to adverse events was 7.7% in the misoprostol group compared with 3.9% in the omeprazole group. Pooling data from both studies showed that the prevalence of GU at relapse was: 9.5% for omeprazole, 10.5% for misoprostol, 16.3% for ranitidine, and 32.2% for placebo. DU at relapse was: 1.7% % for omeprazole, 10.1% for misoprostol, 4.2% for ranitidine, and 12.2% for placebo. Thus, it appears that PPI therapy for NSAID prophylaxis is promising but data showing a reduction in clinical complications is still lacking. However, consideration should be given to PPI therapy for patients requiring NSAIDs who are intolerant of misoprostol.

Although some have suggested a synergistic relationship between HP and NSAIDs, there is no evidence to support that patients infected with HP are at significantly higher risk for PUD when NSAIDs are consumed. Thus, at present, in patients without another indication for HP eradication, there are no data to support testing for and subsequently eradicating HP in patients undergoing routine NSAID therapy.

10) Conclusion

PUD is still a common problem utilizing considerable medical and financial resources. The understanding of the pathogenesis of PUD has been revolutionized by the discovery of HP and the proven efficacy of HP eradication in reducing the recurrence and complications of PUD. The initial approach to a patient suspected of having PUD should include a thorough history and physical to evaluate for the presence of sinister symptoms and signs. NSAIDs should be sought for and discontinued if possible. In younger patients without "red flags," empirical therapy with an antisecretory medication is justified reserving diagnostic imaging or endoscopy for treatment failures or recurrences. Whether to "test and treat" for HP in dyspeptic patients with undocumented PUD based on economic considerations is an evolving strategy that will be refined with more data regarding the efficacy of HP eradication in NUD.

The main question is not who to treat for HP, but rather who to test. Patients who should definitely be tested for HP include previous and active PUD and MALT lymphoma.

Consideration for testing should be given to patients following gastric cancer resection or a strong family history of gastric cancer. Current evidence does not support HP testing in NUD, concurrent use of NSAIDs, long term use of PPIs, or in asymptomatic individuals. However, due to potential ethical and medicolegal issues, HP eradication should be offered to any person testing positive.

Reducing the recurrence of PUD depends on eradicating HP and NSAIDs. Although multiple regimens are now approved, effectiveness of HP therapy is governed by multiple factors including patient compliance and bacterial resistance, and the cost of therapy is governed by the overall efficacy and not initial drug costs. Misoprostol is effective at reducing gastroduodenal injury and complications from NSAIDs but may not be tolerated in a significant proportion of patients. PPIs appear promising as an alternative to misoprostol for NSAID prophylaxis but the results of large, prospective trials are still pending.

References

Available from the author on request

Colorectal Cancer Screening

Maj. Donald A. Weller, MC

Evidence exists that mortality from colorectal cancer (CRC) can be reduced through the identification and removal on adenomatous polyps, the precursors of these cancers. There is also evidence that detection of colorectal cancer at an earlier stage results in improved mortality. The following is designed to offer a guide to current screening options available for CRC, with recommendations for screening and follow up in various groups. There a number of acceptable screening modalities for average risk patients, the choice of options must be individualized to the patient, physician and the practice environment. There are algorithms for CRC in both average and high risk patients at the end of this handout.

I. Statistics

Colon cancer is the second leading cause of cancer death in the U.S. One in twenty persons over age 50 will eventually develop CRC.

-Estimated 131,200 new cases in U.S. in 1997.
-Estimated 54,900 death form CRC in 1997.
-Lifetime Risk 5 %.
-Mortality from CRC has decreased 32 % for women and 14 % for men in last 30 years. Mortality rate for African American men continues to rise.

II. Definitions

Screening: Identifies patients more likely to have CRC or adenomatous polyps from among an asymptomatic population.

Diagnosis: Establishes if those suspected of having CRC truly have the disease or not.

Surveillance: Monitor patients with diagnosed colorectal disease (polyps, CRC, IBD)

III. Principles of screening program

a. Disease is common and associated with significant morbidity or mortality.
b. Screening test accurate, acceptable to patients and feasible in practice.
c. Treatment after early diagnosis improves prognosis over usual.
d. Evidence that benefits outweigh risks.

CRC fulfills all criteria

IV. Risk Factors for CRC

Family History:

One 1st degree relative with CRC	RR 1.72
One 1st degree relative < 45 with CRC	RR 5.37
Two 1st degree relatives with CRC	RR 2.75

Genetic syndromes

Familial adenomatous polyposis (FAP): accounts for 1% cases CRC

Hereditary nonpolyposis colon cancer (HNPCC): accounts for 5% cases CRC.

Defined: 3 or more relatives with CRC; one patient a first degree relative of another; crosses generation; one CRC diagnosed before 50 years.

IV. When and how often to begin screening

High Risk:

1.) Familial Adenomatous Polyposis:
   Genetic Counseling
   Flex Sig every 12 mo beginning at puberty
2.) Family history colon cancer(close family member 1st degree):
   Normal colon cancer screening beginning at age 40 years.
3.) Hereditary Nonpolyposis Colorectal Cancer
   Complete colonic exam (colonoscopy) every 1-2 years starting between age 20-30 years and every year after age 40.
4.) Patients with personal history of adenomatous polyps
   Large (> 1 cm) or multiple polyps: colonoscopy at 3 yrs
   Small or single adenoma : colonoscopy at 5 yrs
5.) People with history of CRC
   Colonoscopy within 1 year of resection, if negative then after 3 years and if again normal every 5 years
6.) Inflammatory Bowel Disease
   Pancolitis: colonoscopy every 1-2 years after 8 years of disease
   Left sided colitis: colonoscopy every 1-2 years after 15 years of disease

Average risk:

Incidence of CRC very low till age 40 then increases thereafter. Screening should be offered to all men and women without risk factors beginning at age 50. There are several alternative modes of screening that are acceptable.

V. Modes of screening for average risk patients

a. FOBT fecal occult blood testing
b. Sigmoidoscopy
c. ACBE
d. Colonoscopy

e. Various combination

A. Fecal Occult Blood Test

Five large prospective controlled studies have demonstrated fecal occult blood testing , with complete colon evaluation in positive cases, results in reduced mortality from colorectal carcinoma.

(Nottingham trial, Univ Minn. trial, Denmark trial)

1. Sensitivity for CRC 72-78% (nonhydrated)
2. Specificity for CRC 98%
3. Positive Predictive Value 10-17%
4. Mortality from CRC reduced 15-33%
5. Yearly testing superior to biannual
6. Less sensitive for adenomas
7. Test :
   - 3 hemoccult cards, 2 windows on each card
   - 3 separate bowel movements
   - 2 samples from each stool, from separate sites
   - dietary restrictions: avoid red meats, turnips, horseradish 2 days prior to collection

Work up of Positive FOBT

If even one panel of a card is positive, ***colonoscop***y should be performed. Repeating the FOBT of performing sigmoidoscopy is not an acceptable alternative. Failure to follow up on positive tests can result in a significant decrease in screening efficacy.

Conclusion

Strong direct evidence of efficacy in mortality reduction.
Detect cancer rather than precancerous lesions (polyps)
Lacks sensitivity
The results of FOBT reflect the performance of a program of repeated screening, not that of a single test.

B. Sigmoidoscopy

A. Effectiveness of sigmoidoscopy in colorectal cancer screening is supported by two case-control studies directly evaluating its use as a screening devise two studies one case-control and one cohort that demonstrated that polyp removal reduces the risk of CRC. CRC mortality reduced 59-80%.

Selby et al. 1992, Newcombe et al. 1992, Muller and Sonnenberg 1995

B. Screening Interval five years currently recommended.

Selby et al. 1992: effectiveness of screening at 10- yr intervals same as more frequent

C. Follow up of positive test with colonoscopy. Any adenomatous polyps or cancer should have follow up. No follow up needed for hyperplastic polyps

D. Disadvantages

detects only approx. 50% of cancers and polyps.
Some risk and discomfort to the patient

Conclusions:

Strong evidence of effectiveness
Detects both cancers and precancerous lesions
Only detects lesions within reach of scope (60cm), limiting overall sensitivity
Screening interval 5 years
Positive screen dictates colonoscopy

C. Barium Enema

There are no studies evaluating ACBE in CRC screening. Potential advantages include its ability to image whole colon. However compared with colonoscopy

ACBE sensitivity less for CRC detection. ACBE sensitivity 83% vs. 95% for colonoscopy. ACBE less sensitive in detecting polyps less than 1 cm. One disturbing study revealed ACBE missed 25% of cancers or polyps > 1cm in the rectosigmoid. If used for screening then intervals of 5-10 years are recommended.

Conclusions:

Offer ability to examine entire colon
Limited sensitivity for smaller lesions, and in rectosigmoid region
No therapeutic potential, positives require colonoscopy.

D. Colonoscopy

Colonoscopy offers the most sensitive and specific test for the evaluation of colon pathology. There have been no randomized studies evaluating colonoscopy as a primary colorectal cancer screening test, in terms of reduced mortality. Indirect evidence would however suggest its efficacy.

1. It has been shown that detection and removal of polyps reduces the incidence of CRC, and that detecting cancers early reduces mortality; colonoscopy can performs this task.

2. Colonoscopy is an integral part of screening plans that have demonstrated mortality reduction.

3. Colonoscopy is comparable to a sigmoidoscopy in effectiveness and performance except it examines the entire colon rather than just the distal 60cm.

Disadvantages

1. Cost (see below) may be greater
2. Involves greater risk than other screening modalities

Conclusion

1. Very sensitive and specific
2. Involves increased risk
3. Evidence to support it use is indirect
4. May be cost prohibitive (see below)
5. An interval of 10 years is recommended for average risk patients

E. Summary of screening test characteristics

Screening Test	Overall Performance	Complexity	Potentiol effectivness	Evidence of effectiveness	Risk
FOBT	Intermediate for CA/Low for polyps	Low	Lowest	Storngest	Lowest
Flexible sigmoidoscopy	High for area examined	Intermediate	Intermediate	Intermediate	Intermediate
ACBE	High	High	High	Weak	Intermediate
Colonoscopy	Highest	Highest	Highest	Weak	Highest
FOBT + Flex Sig	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate

VI. Cost -Effectiveness

The Office of Technology Assessment of the United States Congress recently examined the cost effectiveness of four screening strategies for CRC (FOBT, flexible sigmoidoscopy, ACBE and colonoscopy) both alone and in combination. This analysis revealed that screening of average risk patients for CRC is within the range felt acceptable for screening tests. All strategies cost < $20,000 per year of life saved, which compares favorably with other screening programs.

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Outpatient Lower Gastrointestinal Bleeding

Maj. Terry L. Baldwin, MC

I. Objective: To help primary care providers better understand the proper approach to the evaluation of the outpatient with common types of gastrointestinal bleeding.

II. Introduction: Colorectal carcinoma is the second most common cancer in the U.S. population. Although patients do not always willingly divulge such information to their primary care provider, 16% of patients in one random community survey had noticed rectal bleeding in the preceding 6 months[1]. Much is written about the topic of acute lower gastrointestinal tract bleeding. I would suggest that, although decisions made in these cases require exacting judgment and speed, almost every day we see patients with less sensational bleeding. Such patients, with mild spotting on the toilet paper, or occult gi tract blood loss, require equal precision of judgment to avoid missing pre-malignant lesions at curable stages, or merely to reassure a patient. Colorectal cancer screening, and the topic of occult bleeding, will be addressed by another speaker in this symposium. This presentation will address hematochezia in the outpatient setting.

III. Lower GI Tract Bleeding:

A. Definitions:

1. **LGI tract bleeding -** bleeding distal to the ligament of Treitz.
2. **Outlet-type bleeding** - bright red blood seen during or after defecation, on the toilet paper or in the toilet bowl.

B. Etiologies: the most common causes of **chronic** colorectal bleeding are hemorrhoids, neoplasms, colitis, and angiodysplasia. The most common cause of major **acute** colorectal bleeding is diverticulosis, but neoplasms, radiation injury, ischemia, inflammatory bowel disease (ulcerative colitis and Crohn's disease), solitary rectal ulcer, varices, internal hemorrhoids, endometriosis, and Meckel's diverticulum may present this way.

Table 1 - Causes of Lower GI Tract Bleeding[2]:

Upper GI Tract Bleeding	
Small Intestine	Neoplasm
	Crohn's disease
	Aortoenteric fistula
	Angiodysplasia
	Meckel's diverticulum
Colon	Diverticulosis
	Angiodysplasia
	Neoplasms
	IBD
	Ischemia
	Colitis (infectious, radiation)
	Hemorrhoids
	Fissure

Endometriosis

C. History and Physical: a careful history will often suggest the likely causes of bleeding in a particular patient. For example, an elderly patient would be more likely to be bleeding from angiodysplasia or diverticulosis, while a younger patient would be more likely to bleed from hemorrhoids, anal fissures, or inflammatory bowel disease.

Table 2. Diagnostic Hints for Lower GI Tract Bleeding[2]:

Symptom	Possible Diagnosis
Abdominal pain	Ischemic bowel
	IBD
	Ruptured aortic aneurysm
Painless bleeding	Diverticuli
	Angiodysplasia
	Hemorrhoids
Bloody diarrhea	IBD
	Infection
Rectal pain	Anal fissures
	Hemorrhoids
Constipation	Malignancy
	Hemorrhoids

Of course, the patient should initially be evaluated for hemodynamic stability. History will indicate whether the bleeding is a chronic, slow process, an acute yet mild process, or a brisk bleed. The latter would obviously not be appropriate for continued management in the outpatient setting. Physical examination clues may indicate the severity of bleeding, with postural hypotension indicating a 20% blood loss, and pallor, hypotension, and tachycardia indicative of a 30-40% blood loss.

In patients without evidence of an acute, hemodynamically significant bleed, certain diagnostic clues are often used to guide the subsequent outpatient evaluation. Traditionally, factors such as age, family history of colon cancer, or probable location of bleeding ("outlet bleeding" vs. upper colonic source) have been used to guide the choice of sigmoidoscopy vs. full colonoscopy. This having been said, however, there is little evidence that a physician's prediction of the bleeding source based on symptoms has enough accuracy to limit the evaluation of any given patient. Mant *et al.* evaluated 145 patients aged 40 years and older who underwent total colon examination after presenting with rectal bleeding. Of 15 symptoms studied, only the finding of blood mixed with feces had an elevated risk of colorectal carcinoma (21%, vs. 11% overall)[3]. In a previous study, the same group reported that the general practitioner's prediction of an anal vs. colorectal source of bleeding was inaccurate[4]. This finding was recently reaffirmed by Segal *et al.*, who studied 103 outpatients aged 45 years or greater with hematochezia. Each patient completed a detailed interview, including factors such as type of bleeding, amount of bleeding, duration of bleeding, weight loss, and personal and family history of GI problems. Physicians were asked to predict whether bleeding was from a perianal or more proximal site, and all patients underwent anoscopy and colonoscopy. Clinicians were unable to predict substantial pathology based on symptoms alone. Of interest, flexible sigmoidoscopy would have detected 95% of substantial lesions in this study, and all cancers[5]. Before concluding that

flexible sigmoidoscopy is an adequate evaluation for all patients with rectal bleeding, it should be appreciated that the incidence of colorectal cancer in this series (4%) was lower than that presented by other authors.

D. Evaluation of Lower Gastrointestinal Bleeding: it is impossible to present an absolute, evidence-based approach that works for all patients with LGI bleeding. Controversies exist as to the appropriate management of "outlet-type" bleeding, and what is the preferred method of total colonic assessment when this is deemed appropriate (ACBE + flexible sigmoidoscopy vs. colonoscopy). The following approach is based upon current consensus opinion, as well as such evidence that is currently available:

1. **History and Physical**: assess severity of bleeding, need for inpatient evaluation/resuscitation, diagnostic clues. ALL PATIENTS
2. **Nasogastric aspiration**: in patients with severe bleeding (10-15% of LGI bleeding actually arises proximal to Ligament of Treitz). PATIENTS WITH SEVERE BLEEDING
3. **Upper GI Endoscopy**: If NG lavage is positive, or if upper source cannot be excluded (a nonbilious clear lavage does not exclude a bleeding DU, for example). SOME PATIENTS WITH SEVERE BLEEDING
4. **Flexible Sigmoidoscopy**: In low-risk patients (age < 40, no personal or first degree relatives with colorectal cancer, no blood mixed with stool) with "outlet-type" bleeding. SELECT PATIENTS WITH MILD BLEEDING
5. **Colonoscopy**: Is diagnostic modality of choice for high-risk patients with mild bleeding (age > 40, personal or family history of colorectal cancer, blood mixed with stool) and in patients with severe bleeding with negative UGI evaluation (as "purge" colonoscopy) MOST PATIENTS WITH MILD OR SEVERE BLEEDING
6. **Scintography**: patients with ongoing bleeding with negative colonoscopy may have scan following injection of technicium-99m-labeled rbcs. May help localize bleeding site with bleeding rates of 0.1ml/min or less. This is often used as screening prior to angiography. SELECT PATIENTS WITH ONGOING ACUTE/SEVERE BLEEDING
7. **Angiography**: patients with ongoing bleeding, unhelpful colonoscopy, and positive scintography (per most current protocols) may reveal extravasation of contrast media with arterial bleeding rates as low as 0.5 ml/min. This may also allow therapeutic infusion of vasopressin, or transcatheter embolization. Limitations include need for active bleeding and high complication rate. SELECT PATIENTS WITH ONGOING/SEVERE BLEEDING
8. **Enteroclysis**: often used in patients with GI bleeding when neither UGI or colonic source is revealed. Yield overall is 10%, but may be as high as 20% in patients with a well-performed UGI and colon examination that were normal[6]. SELECT PATIENTS WITH ONGOING BLEEDING

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Evaluation of Abnormal Liver Function Tests

Maj. Steven J. Bindrim, MC

Introduction

Unexpected elevations of routine liver test values in asymptomatic patients discovered during routine blood donor screens or serendipitously on labs performed for other indications are commonly encountered in clinical practice. A systematic approach towards the identification of the cause of the abnormal tests revolves around obtaining a thorough medical history and the performance of a physical exam directed towards clues indicating the presence of liver disease. The history and physical exam as well as the pattern of liver test abnormalities (hepatocellular vs cholestatic) in concert with radiologic and more specialized blood tests will often provide the diagnosis. If the aforementioned evaluation does not provide a diagnosis, liver biopsy in many cases will.

Clinical Assessment

As with the evaluation of any medical problem a thorough medical history and physical exam is the foundation of the work-up.

Medical History

Key issues to be addressed in the medical history would include the determination of how long the liver test abnormalities may have been present. This can sometimes be established in patients who have been regualr blood donors in the past and are suddenly rejected by the red cross. Occasionally review of prior medical records and past lab tests will reveal abnormal liver tests not previously addressed. Episodes of symptoms consistent with acute hepatitis (jaundice, RUQ abdominal pain with or without nausea and vomiting, fevers, fatigue, clay colored stools, dark urine) in the past (or present) should be questioned as well.

Risk factors for the acquisition of viral hepatitis (primarily hepatitis C or B +/- D) should be sought and would include such factors as prior intravenous drug abuse, blood transfusions, sexual promiscuity or sexual relations with a person known to have hepatitis, needle stick injuries, and the placement of tattoos.

Risk factors for Hepatitis A (which does not result in chronic hepatitis but can result in a relapsing form that can last up to 8 months or longer) would include overseas travel to third world countries and employment in day care centers, as well as the consumption of raw oysters.

The past medical history can be extremely helpfull in elucidating the cause of the abnormal liver tests and would include alcohol consumption (more helpful if corroborated by a family memeber), and illicit drug use.

Chronic medical problems should be established as many of these can contribute to liver disease. For example diabetes mellitis, obesity, and hyperlipidemia are established risk factors for the development of nonalcoholic steatohepatitis (NASH) which is a very common cause of

elevated liver function tests. Other medical problems of interest would include the presence of inflammatory bowel disease (associated with Primary Sclerosing Cholangitis), cardiac disease (associated with hemochromatosis or congestive hepatopathy). Autoimmune induced diseases such as rheumatoid arthritis, Sjogren's syndrome and thyroid disease can be associated with autoimmune hepatitis or Primary Biliary Cirrhosis.

A prescription drug history (including over the counter meds) can be one of the most valuable parts of the medical history. A majority of medications including such seemingly inocuous drugs such as aspirin, birth control pills, and certain antibiotics can result in the elevation of liver tests.

A family history of liver disease could indicate potential inheritable forms of liver disease to include hemochromatosis (iron storage disease), Wilson's disease (copper storage disease), or alpha 1 antitrypsin deficiency.

A review of symptoms directed at such questions as chronic fatigue, anorexia, loss of desire to smoke, unexplained weight loss and abdominal pain should be sought as well.

Physical Exam

The physical exam can be helpful in establishing the presence of chronic liver disease. Physical exam findings would include the presence of jaundice (icterus) which is most easily detected in the sclera and frenulum of the tongue. Muscle wasting should also be sought which often can be seen in the temporal areas of the skull (temporal muscle wasting) as well as in the extremities. Other prominant signs would include a protuberant abdomen indicating possible ascites, and caput medusa indicating portal hypertension.

In males, the presence of gynecomastia, testicular atrophy and loss of axillary hair would be indicative of possible cirrhosis, which probably results from the conversion of weakly androgenic steroids to estrogen steroids in the peripheral tissues.

Other subtle signs of chronic liver disease would include the presence of spider angiomas most commonly located on the chest, neck, upper extremities and face. The hands can reveal such signs as palmer erythema, Dupuytren's contractures and "liver nails".

Abdominal exam should focus on the size and contour of the liver as well as for the presence of a bruit over the liver (indicating possible hepatocellular carcinoma). Other findings to be sought would be the size of the spleen and the presence of shifting dullness or circussion splash indicating the presence of ascites.

Lower extremity edema could indicate cirrhosis resulting in portal hypertesion or obstruction of the inferior vena cava.

Kayser-Fleischer rings indicate Wilson's disease.

Interpretation of Liver Tests

The pattern of elevation of the liver tests helps narrow the differential diagnosis as to the etiology of the liver disease. In general two patterns of liver injury can be seen; hepaocellular or cholestatic.

Cholestasis simply defined means cessation of bile flow and can be further subdivided into intrahepatic (at the level of the intrahepatic bile ducts) and extrahepatic (from the level of the hepatic hilum distally to the duodenum). Cholestatic processes result in an elevation of the alkaline phosphatase with or without concomittant elevations in the bilirubin level.

Hepatocellular injury reflects damage to the hepatocytes themselves with resultant increases in the transaminase levels.However, before discussion of patterns of liver test abnormalities it is important to understand what each test represents.

Aminotransferases

Otherwise known as transaminases, include AST (formerly known as serum glutamic-oxaloacetic transaminase or SGOT) and ALT (formerly known as serum glutamate pyruvate transaminase or SGPT), and are perhaps the most sensitive indicators of hepatocyte injury.

The transaminases are involved in the transfer of amino groups of aspartate and alanine to ketoglutaric acid for the synthesis of glucose from noncarbohydrate sources.

The AST enzyme is found both in the mitochondria and cytosol of hepatocytes. However AST is also present in cardiac, skeletal, kidney, and brain tissue. Therefore an isolated elevation of AST in an otherwise normal liver test panel should prompt an evaluation of nonhepatic sources (such as cardiac or muscle diseases).

The ALT enzyme is present almost exclusively in the liver and is a better index of liver cell injury. It is also present in the hepatocyte cytosol only.

The ratio of AST to ALT can be a useful marker to diagnose specific liver diseases.

In alcoholic hepatitis the AST : ALT ratio is greater than 2, and the AST increase is not more than 300 U/L.

In viral hepatitis the ratio of AST to ALT is typically less than 1.0 but rises, often to levels greater than 1.0 as cirrhosis develops.

Alkaline Phosphatase

Alkaline phosphatase is actually a family of isoenzymes that catalyze the hydrolysis of a number of phosphate esters at an alkaline pH optimum. It is present in bone, placenta, intestine, kidney, and liver tissue, however, more than 80% of circulating alkaline phosphatase is in the liver and bone.

Liver alkaline phosphatase is synthesized by the bile duct epithelial cells. The response to obstruction of bile ducts is increased synthesis and release of alkaline phosphatase. This outcome can result even if the obstruction is in a few small bile ducts and is insufficient to cause an increase in bilirubin.

An increase in the alkaline phosphatase levels is generally associated with increased GGT or transaminase levels. If the alkaline phosphatase level alone is elevated and the etiology (hepatic vs nonhepatic) is unclear, fractionation of the alkaline phosphatase may be performed. A 5' nucleotidase level may be obtained as well and if it is increased would indicate hepatic origin of the alkaline phosphatase.

Many different disease processes can result in hepatic damage and increased alkaline phosphatase levels.

Extrahepatic causes most commonly would include choledocolithiasis as well as bile duct strictures and pancreatic or ampullary tumors.

Intrahepatic causes most commonly include drugs with erythromycin, thiazides chlorpromazine, estrogens, captopril, diflunisal and haldol being some of the more common culprits. Other causes include granulomatous or infiltrative diseases of the liver to include sarcoidosis, fungal infections, tuberculosis, lymphoma, hepatocellular carcinoma, and any

metastatic cancer to the liver. Primary Biliary Cirrhosis which commonly occurs in middle aged women and results from the progressive destruction of intrahepatic bile ducts (with a positive anti-mitochondrial antibody being the hallmark) is another cause.

Primary Sclerosing Cholangitis which commonly occurs in young adult males results from the destruction of both intra and extrahepatic bile ducts and results in an increased alkaline phosphatase level.

Bilirubin

The total bilirubin level is usually less than 1.1 mg/dl, and approximately 70% is indirect (unconjugated). If more than 80% of the total bilirubin is indirect, the entitiy is termed "unconjugated hyperbilirubinemia" with the most likely etiologies being hemolysis or Gilbert's Syndrome. In hemolysis or Gilbert's Syndrome bilirubin levels are less than 6 mg/dl.

If more than 50% of the total bilirubin is direct bilirubin the state is termed "conjugated hyperbilirubinemia" and indicates either hepatocellular dysfunction or cholestasis.

In common bile duct obstruction secondary to gallstones, it is unusual for the bilirubin level to increase to more than 15 mg/dl because the obstruction is generally incomplete; it is usually less than 6 mg/dl.

Prothrombin Time

The vitamin K-dependant clotting factors include factors II, VII, IX, and X, and are produced in the liver. The prothrombin time may be prolonged if vitamin K is not absorbed (due to cholestasis) or in the presence of severe hepatocellular disease. If the prolongued prothrombin time is due to cholestasis, a more than 30% correction is noted in the prothrombin time 24 hours after parenteral administration of vitamin K. The prothrombin time can be prolonged in patients with severe liver disease of only 24 hours duration. It is a far more sensitive index of liver synthetic function than is albumin.

Patterns of Elevated Liver Test Abnormalities

Hepatocellular Injury

Results from the destruction of the hepatocytes with the resultant disruption of the plasma membranes and release of the aminotransferases AST and ALT into the blood stream. While the AST and ALT are elevated in most forms of liver disease, their highest concentrations are found in patients with pure hepatocellular disease.

Mild persistant elevations in the 2-5 fold elevated range are characteristic of chronic viral hepatitis, steatohepatitis, and metabolic diseases such as Wilson's disease or hemochromatosis.

Extremely high levels (generally defined as greater than 10 fold and ocassionally as high as 10,000 U/L) are generally seen with acute viral hepatitis, ischemic hepatitis, and drug induced hepatitis (most commonly acetaminophen with or without alcohol).

It should also be kept in mind that the alkaline phosphatase levels may also be elevated in hepatocellular type liver disease, but the elevation is usually mild (less than 2-3 fold elevation).

In moderate to severe hepatocellular injury the bilirubin level may be elevated as well.

Cholestatic Liver Injury

Cholestatic liver injury is characterized biochemically by greater elevation in the serum alkaline phosphatase level or serum conjugated bilirubin level than in the aminotransferase levels. Alkaline phosphatase is a component of the hepatocyte canalicular membrane, and the retention of bile salts due to cholestasis (cessation of bile flow) induces the synthesis of alkaline phosphatase by the hepatocyte. The alkaline phosphatase then regurgitates back into the sinusoids and into the blood stream. Alkaline phosphatase levels are generally elevated in the 3-5 fold range in cholestatic liver disease.

Bilirubin levels may or may not be elevated, and elevation of both the alkaline phosphatase and conjugated bilirubin levels while relatively nonspecificis seen most often with biliary tract obstruction. The serum aminotransferases if elevated are usually less than 2-3 fold elevated.

Evaluation of the Patient with Abnormal Liver Tests

A thorough history, physical examination, and biochemical liver tests are generally sufficient for making an accurate diagnosis of the type of liver disease in approximately 80% of patients.

A couple of clinical "pearls" will help in the evaluation of abnormal liver tests.

The first is that an isolated elevation of the ALT in an otherwise healthy patient if repeated will be normal in 33-50% of patients.

If an abnormal liver test is encountered, it is preferable to repeat the liver panel (to include an AST, ALT, alkaline phosphatase, total bilirubin, GGT, and albumin level) with the patient fasting overnight, and without having consumed any alcohol for 72 hours.

A good rule of thumb is to confirm each abnormal liver test with another test. For example an AST increase should be confirmed by an ALT increase. An increase in the alkaline phosphatase should be confirmed by either fractionation of the alkaline phosphatase, or by obtaining a GGT or 5' nucleotidase. If either are elevated then the alkaline phosphatase is most likely of hepatic origin. To expedite the evaluation a full liver panel may be obtained as above.

Another reason to obtain a full liver test panel is to determine if the liver disease is of an hepatocellular, cholestatic or mixed type.

Hepatocellular Liver Disease

Common causes of hepatocellular injury (aminotransferases are predominantly elevated) in the asymptomatic patient would include chronic viral hepatitis B (with or without concommitant delta hepatitis infection), chronic hepatitis C, autoimmune hepatitis, drugs, nonalcoholic steatohepatitis, hemochromatosis, and alcohol use.

Hepatitis B

Risk factors for the acquisition of hepatitis B would include prior drug transfusions, needle stick injuries, intravenous drug use, and sexual promiscuity. Although 95% of people with acute hepatitis B resolve the infection, 3-5% will go on to a chronic state. This is reflected by aminotransferase levels that may be minimally elevated to levels 10 fold or greater. The ALT to AST ratio is usually >1, but with the development of cirrhosis may become < 1, and the alkaline phosphatase level tends to increase mildly as well.

In patients with resolution of the hepatitis B infection, the panel will reveal positive hepatitis B surface antibody (HBsAb +), as well as a positive hepatitis B core IgG antibody (HBcAb +

[IgG]). Both the hepatitis B surface antigen (HBsAg -), and hepatitis B e antigen (HBeAg -) should be negative.

In patients with chronic hepatits B the surface antigen will be positive (HBsAg +) the surface antibody will be negative (HBsAb -), and the e antigen may or may not be positive.

Patients previously vaccinated with the hepatitis B vacccine will be positive for the hepatitis B surface antibody only (HBsAb +).

Evaluation of an asymptomatic patient with elevated aminotransferase levels with risk factors for the acquisition of hepatitis B should include a hepatitis B surface antibody and antigen as well as a core IgG antibody.

Hepatitis C

Like hepatitis B risk factors for the acquisition of hepatitis C would include prior blood transfusions, needle stick injuries, and intravenous drug use. Although it appears that hepatitis C may be transmitted sexually, it appears to occur rarely, unlike hepatitis B where the virus is transmittted much more efficiently through sexual relations.

Unlike hepatitis B, 85% of patients infected with hepatitis C will develop a chronic infection, of which approximately 30-40% will develop cirrhosis over an approximately 20 year period.

Serum aminotransferase levels may be persistantly normal in up to 1/3 of patients with chronic hepatitis C infection, or may range from minimaly elevated up to 10 fold or greater. In the majority of patients the aminotransferases will fluctuate up and down over time, and generally run from1 1/2 to 4 times normal.

Diagnosis is achieved by obtaining an anti-HCV antibody (EIA method). This can be confirmed by obtaining a RIBA, or by checking a hepatitis C RNA (qualitative) by the PCR method. At least 90% of patients with chronic hepatitis C are viremic, however some are only intermittently viremic.

Autoimmune Hepatitis

Three types of autoimmune hepatitis exist, although Type I is by far the most common. Autoimmune hepatitis also accounts for approximately 80% of nonviral chronic hepatitis in adults in the U.S. Type I hepatitis generally occurs in females age 40 years or younger. The diagnosis generally rests on a positive antinuclear antibody (ANA) or a positive anti smooth muscle antibody (ASM), although not all patients with autoimmune hepatitis will be positive for either.

Drugs

Drugs are a very common cause of asymptomatic elevations of the aminotransferases and include anticonvulsants (phenytoin, valproic acid), analgesics (acetominophen, diclofenac, ibuprofen, salicylates), antimicrobials (isoniazid, rifampin, tetracycline, sulfonamides, quinolones) cardiovascular medications (amiodarone, alpha-methyldopa, hydralazine, quinidine, lovastatin, sustained release niacin) and most tricyclic antidepresant drugs to name a few.

Nonalcoholic Steatohepatitis

The excess deposition of fat in the liver (steatosis) may result in hepatitis with elevations of the aminotransferases predominantly although the alkaline phosphatase levels may be increased up to two fold as well. Risk factors for the development of nonalcoholic steatohepatitis

include obesity, diabetes mellitis, hyperlipidemia, and jejuno-ileal bypass surgery. Abdominal ultrasound generally will reveal an increased echogenicity of the liver, but diagnosis generally is conclusively obtained by liver biopsy.

Hemochromatosis

Hemochromatosis is an iron storage disease where excess iron is absorbed from the diet from birth resulting in an excess accumulation of 500 - 1,000 mg of iron per year. The iron is preferentially deposited in the liver, pancreas, heart, and other organs. Clinical manifestations include skin hyperpigmentation (bronze diabetes), hepatomegally, and arthropathy. Patients generally become symptomatic in the 5th and 6th decades of life. The aminotransferases are the most common liver test abnormality but are rarely greater than two fold elevated.

Laboratory screening includes iron studies and serum ferritin 6evels. A serum ferritin level greater than 500 with an iron saturation greater than 50% is 94% sensitive for the diagnosis. Suspician should be raised in females with an iron saturation greater than 50% an in males greater than 60%. The serum iron studies must be obtained in a fasting state. The gold standard for diagnosis includes obtaining a liver biopsy where a portion of the liver is sent for quantitative iron concentration. This iron concentration is adjusted for by the patients age yielding an iron index. An iron index of 2 or greater clinches the diagnosis.

Alcohol

Excess alcohol consumption resulting in alcoholic hepatitis can also cause a rise in the aminotransferase levels and in severe cases can result in alkaline phosphatase and bilirubin elevations. The GGT will be elevated in many cases as well.

Diagnostic clues include an AST : ALT ratio of two or greater with the AST levels rarely exceeding the 300's. An ALT level greater than 300 is almost never seen in alcoholic hepatitis and should prompt an evaluation for another diagnosis.

It should also be kept in mind that significant liver damage may occur in alcoholics who consume even moderate amounts of acetominophen, and the combination can result in transaminase levels in the thousands.

Cholestatic Liver Disease

Cholestasis simply defined means cessation of bile flow. This can occur at the level of the hepatocyte or the intrahepatic bile ducts (intrahepatic causes) or at the level of the extrahepatic ducts from the hilum of the liver to the ampulla. Some disease processes effect both the extra and intrahepatic bile ducts such as Primary Sclerosing Cholangitis.

Intrahepatic Causes

Drugs

A common cause of intrahepatic cholestasis would include many prescription drugs to include antimicrobials (semisynthetic penicillins, erythromycin, nitrofurantoin), analgesics (diflunisal), antihypertensives (thiazide diuretics, captopril), anticonvulsants (carbamazepine), psychotropics (chlorpromazine, haloperidol), and C-17 alkylated anabolic and contraceptive steroids.

Primary Biliary Cirrhosis

Primary Biliary Cirrhosis (PBC) is a chronic progressive disease that results from the destruction of the intrahepatic interlobular and septal bile ducts. The disease occurs predominantly in middle aged females (median age 50-55). The most common presenting symptoms are pruritis and fatigue. Approximately 90-95% of patients are positive for the anti-mitochondrial antibody (AMA) on which the diagnosis is based (along with a liver biopsy in most caes).

Various Causes

Various other causes of intrahepatic cholestasis are listed below, although these will probably not be encountered routinely in the outpatient clinical setting.

Administration of total parenteral nutrition
Extrahepatic bacterial infections
Idiopathic cholestasis of pregnancy
Idiopathic benign recurrent cholestasis
Hodgkins Disease

Extrahepatic Causes

Choledocolithiasis is the most common cause of extrahepatic biliary obstruction. This generally results in bilirubin levels in the 2-5 mg/dl range and is rarely greater than 12 mg/dl. Right upper quadrant or epigastric pain is often present, and the jaundice is generally transient, but on occasion may last a longer period of time. A potential complication would include the development of bacterial cholangitis which generally presents with jaundice, high fevers, chills, right upper quadrant pain, and in severe cases hypotension and shock.

Primary Sclerosing Cholangitis

PSC is a chronic cholestatic liver disease of unknown cause characterized by ongoing inflammation, destruction, and fibrosis of the intra and extrahepatic bile ducts. It generally occurs in young males. The gold standard for diagnosis is an ERCP.

Pancreatic Disease

Acute pancreatitis may result in swelling of the pancreatic head resulting in partial obstruction of the intrahepatic portion of the common bile duct, but this rarely results in jaundice. If a patient does present with acute pancreatitis and jaundice it is imperative to rule out an impacted gallstone in the distal common bile duct as a cause of the pancreatitis and jaundice (gallstone pancreatitis).

Chronic pancreatitis can result in partial or total distal common bile duct obstruction due to fibrotic narrowing of the intrapancreatic portion of the common bile duct, or by compression from a pseudocyst.

Various Causes of Extrahepatic Cholestasis

Parasitic diseases of the common bile duct
Choledocal cysts

Ampullary Carcinoma
Duodenal diverticula
Duodenal Crohn's disease
Hepatic artery aneurysm
Blunt abdominal trauma
Cholangiocarcinoma
Caroli's disease

Evaluation Of Elevated Aminotransferases

Please refer to algorithm 1.

As stated previously a thorough history and physical exam is a major component of the evaluation of abnormal liver tests. It is also helpfull to order a complete liver test panel (AST, ALT, alk phos, total bili, and GGT) early in the evaluation as this willl determine if a strictly hepatocellular process vs a mixed hepatocellular and cholestatic process exists.

If signs of chronic liver disease (muscle wasting, palmer erythema, Dupuytren's contractures, ascites, spider angiomas, gynecomastia etc) are found on physical exam it would be most prudent to obtain a full lab panel (serum iron, TIBC, ferritin, hepatitis C antibody, hepatitis B core antibody [IgG], surface antibody and surface antigen, antinuclear antibody, anti smooth muscle antibody, ceruloplasmin level [if under 50 years old], and alpha 1 antitrypsin level) unless the patient admits to a long history of alcohol abuse and the AST is at least two times the ALT level.

If no signs of chronic liver disease are present then it should be determined if alcohol or potential medications are causing the abnormal aminotransferase levels. If this is a potential cause, the possible offending drug, or alcohol use should be discontinued and the liver tests rechecked in 4 weeks. If the liver tests normalize no further evaluation would be warranted. If the liver tests remain abnormal a full lab evaluation and a liver ultrasound should be performed and the patient should probably be referred to a gastroenterologist.

If alcohol and medications are not a potential cause, then obesity or a significant recent increase in weight should be ascertained. If this appears to be an issue, the patient should be encouraged to lose 10% of their body weight over a 3 to 4 month period and have liver tests rechecked at that time. If the liver tests normalize then no further evaluation is required. If they don't normalize then a full lab evaluation should be performed.

If neither alcohol, drugs, or obesity appear to be a potential cause, then a full lab evaluation should be performed up front, with probable referral to a gastroenterologist upon return of these test results.

Evaluation Of Alkaline Phosphatase Elevation

If an isolated alkaline phosphatase level is found, the test should be repeated in a fasting state since patients with blood groups O or B and are secreters may have elevated levels after fatty meals secondary to release of intestinal alkaline phosphatase. If the repeat level is normal, no further evaluation is required. If the repeat level is still elevated then an hepatic source should be confirmed by either fractionating the alkaline phophatase or obtaining a GGT level (a full liver panel would be helpful as well). If the tests reveal a nonhepatic source for the elevated alkaline phosphatase, then an evaluation for extrahepatic sources should be sought.

If an hepatic source is verified then possible drug induced cholestasis should be investigated. If drugs are a possible etiology, they should be discontinued and liver tests should be repeated in 2 to 4 weeks. If the tests normalize no further evaluation is required. If the alkaline phosphatase level does not normalize or no drugs can be implicated then an abdominal cat scan (if a pancreatic etiology is suspected) or ultrasound should be obtained. If dilated ducts are noted on the radiologic studies then the patient should be referred to a gastroeterologist for consideration of an ERCP. If dilated ducts are not found but liver mass(es) are found, the patient should undergo ultrasound or CT guided biopsy. If no dilated ducts or liver masses or lesions are noted then an antimitochondrial antibody should be obtained and the patient should be referred to a gastroenterologist.

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Irritable Bowel Syndrome

Maj. Stephen M. Schutz, MC

Introduction

The Irritable Bowel Syndrome (IBS) is an entity characterized primarily by abdominal pain and altered bowel habits. Since patients with IBS may present in a wide variety of ways in individual patients, a set of diagnostic criteria has been developed.[1] (see algorithm)

Although a diagnosis of IBS may be arrived at after extensive testing to exclude other organic gastrointestinal diseases, IBS is not a true, "diagnosis of exclusion". An understanding of this concept is important for clinicians, who might otherwise be tempted to order batteries of expensive (and potentially risky) lab and x-ray tests.

Epidemiology

IBS symptoms are common in adults, reported in 10-22% of healthy individuals in questionnaire studies. There is no age predilection in IBS, though most patients report the onset of symptoms in young adulthood. Interestingly, of adults with symptoms consistent with IBS, only about 20-30% seek medical attention.[2] Despite this low percentage, though, IBS accounts for as many as 25-50% of outpatient referrals to Gastroenterologists.[3]

Pathogenesis

The pathogenesis of IBS is unknown. Most studies to date indicate that GI dysmotility or abnormal visceral sensation are involved in causing the varied signs and symptoms of IBS. In addition, it appears that psychosocial factors play an important role in this disorder. While actual psychopathology is no more prevalent in individuals with IBS symptoms than it is in the general population, it is more common in patients with IBS who seek medical care.[4-6]

Stress does not cause IBS, but it does result in exacerbations. Patients with IBS frequently – but not always – report increased symptoms during stressful periods. As is the case with the etiology of IBS proper, it is not known why stress increases symptoms in patients with IBS.[6]

Diagnosis

The initial evaluation of any patient presenting with abdominal pain and altered bowel habits must include a thorough history and physical examination. Signs and symptoms consistent with the established diagnostic criteria (see algorithm) should bring reassurance to a clinician – when they are present, a positive diagnosis of IBS is likely.

Abdominal pain: typically lower abdominal in location, but may occur in any region of the abdomen. Frequent descriptors include "crampy", "gassy", or "bloating".

Altered bowel habits: normal = 3BM/wk to 3BM/day. An alteration in stool frequency represents a deviation from that norm. An alteration in stool character may take many forms (see algorithm).

- A common event for IBS patients is passage of small "pebbly" stools. Passing mucus is also typical.
- Lactose intolerance and the side effects of many medications may cause altered bowel habits. These possibilities should be sought carefully in any patient under evaluation for possible IBS.

Care should always be taken to exclude symptoms suggestive of organic disease, such as:

- pain that awakens patient from sleep
- pain that interferes with normal sleep patterns
- diarrhea that awakens patient from sleep
- gross or occult blood in stool
- presence of weight loss or fever

The physical examination in IBS is generally unremarkable. Mild abdominal tenderness or distention may be noted, however.

Laboratory studies should include simple screening tests only, to include a SMA 12, CBC, and ESR. If diarrhea is a prominent feature of the history, then stool examination for O&P, enteric pathogens, and WBC count are reasonable. If there is any reason to suspect thyroid disease by H&P, then TFTs should be ordered as well. All average risk patients over the age of 40 should undergo FOB testing and flexible sigmoidoscopy to screen for colon cancer or large polyps. Those with a family history of colon cancer (first degree relative) should be referred to GI for colonoscopy. Younger patients with chronic diarrhea and any evidence to suggest ulcerative colitis should also undergo flexible sigmoidoscopy to evaluate the colonic mucosa.

Treatment

The first line of therapy for IBS is reassurance. Many, if not most, IBS patients harbor a fear of cancer, so a positive discussion highlighting the benign nature of IBS should be undertaken as soon as the diagnosis is arrived at. It is therapeutic for patients to hear from a clinician that their symptoms are not, "all in their head", but actually represent a real clinical entity. Patients should also be informed that IBS is common and carries an excellent prognosis.[7] Once that discussion has taken place, longitudinal follow up should be continued. A physician-patient relationship that extends over time has important therapeutic value, as well.

While reassurance and a relationship with the patient over time are the most important therapeutic interventions, dietary improvements should also be strongly encouraged. A high fiber diet and/or the use of supplements such as psyllium are generally recommended, but their actual efficacy may be somewhat difficult to gauge due to the high placebo response rate IBS –

as high as 63-71% -- seen in IBS.[4] One prospective study looking at first-line therapy for IBS found that most patients responded, and two thirds remained symptom free after five years.[8]

If reassurance and dietary intervention fail or a symptom flare develops later, second-line therapy should be tailored to the predominant feature of the individual patient's complaints:

- Constipation-predominant IBS: add fiber and/or MOM (if the patient is already on fiber, the importance of drinking extra fluids with the fiber should be emphasized).
- Pain-predominant IBS: add antispasmotics (see algorithm).
- Diarrhea-predominant IBS: add fiber without extra PO fluids. Consider Imodium or antispasmotics.

Patients with refractory symptoms that either do not respond to the first- and second-line interventions noted above or flare frequently should be referred to Gastroenterology for further evaluation. It bears repeating, though, that the proportion of refractory patients in the IBS pool is quite small.

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Inflammatory Bowel Disease

"Managing IBD Before It Manages You"

Maj. Kevin Lang, MC

Overview

The management of inflammatory bowel disease can be daunting and confusing. Treatment modalities are numerous and some are controversial. Enthusiasm is often tempered by the fact that no cure exists for either Crohn's Disease (CD) or Ulcerative Colitis (UC); short of colectomy for UC, that is. The purpose of this lecture and handout is to help you make relatively quick, accurate, and focused assessments of inflammatory bowel disease patients in brief clinic appointment times.

The following is an abbreviated overview of management issues that should be in the back of your mind when a patient with IBD comes into your office.

ULCERATIVE COLITIS

Management issues:
- Duration of disease
- Extent of disease
- Clinical severity
- Medications and dosages
- Neoplasia risk
- Associated conditions
  - Primary sclerosing cholangitis
  - Arthritis

CROHN'S DISEASE

Management issues:
- Location (gastroduodenal, small bowel, colonic, combination)
- Extent (localized/extensive)
- Type (inflammatory/stenotic/fistulizing)
- Prior surgery
- Duration of disease
- Clinical severity
- Medications and dosages
- Neoplasia risk
- Associated conditions
  - Primary sclerosing cholangitis
  - Arthritis

The diagnosis of CD or UC will not be discussed. Rather, I will direct your attention to management and surveillance issues. First, let us consider the patient with UC.

CASE 1

29 y/o AD male with UC diagnosed 4 years ago comes to your clinic as a new patient. He is presently asymptomatic and is not taking any medication. He is a lab technician at Wilford Hall.

Questions:
1. How would you classify his disease activity?
2. Should he be on maintenance therapy?
3. What interval should he f/u with you?
4. Does he need any additional testing?
5. If he has never had an MEB should he get one? Why or why not?
6. Should he begin surveillance colonoscopy at this time? If not now, when?

CASE 2

35 y/o AD female pilot with UC diagnosed 2 years ago. Was doing well until a week ago when she started having eight bloody/mucous bowel movements daily with mild LLQ abdominal pain. On your exam she is non-toxic appearing, T 99.9 F, with mild tenderness in her LLQ. Review of her medications shows she is taking Asulfadine 2 g daily in divided doses.

Questions:
1. How would you classify her disease activity at the present time?
2. What medication adjustments could you make?
3. Do you need to refer her to GI now?
4. What administrative actions should you think about?
5. What follow up interval will you choose to reassess her clinical status?

CASE 3

32 y/o female with Crohn's disease diagnosed 6 years ago with the following characteristics:

1. Location: ileocecal
2. Extent: localized
3. Type: inflammatory
4. Prior surgery: none

She is presently asymptomatic and is taking no medications.

Questions:
1. How would you classify her disease activity?
2. Should she be on maintenance therapy?
3. What interval should she f/u with you?
4. Does she need any additional testing?
5. She is considering pregnancy, is it contraindicated, she asks?

CASE 4

26 y/o AD F-16 pilot with localized jejunal and colonic Crohn's disease diagnosed 4 weeks ago. He presents to your clinic with nausea and vomiting for 48 hours and has had subjective fevers at home. He is taking Pentasa 4.0 g daily in divided doses, no other medications. On exam T 100.9, mildly toxic appearing with orthostatic vital signs. Bowel sounds faint, high pitched with tinkling. Just lateral to his umbilicus he has a draining fistula which he said he first noticed 2 days ago KUB shows multiple AFLs in the small bowel.

Questions:
1. How would you classify his disease activity?
2. What should you do next?

Table 1. Inflammatory Bowel Disease Medication Checklist- Dosages and Indications

Checklist for Inflammatory Bowel Disease	**Yes**	**No**	**Action (for any "yes" response)**
Medications			
Dose inadequate? See Table 2 or 3			Adjust dose
Wrong medication for disease site? See Table 2 or 3			change medication/GI help
Unable to taper steroids (>6 months)?			GI referral

Table 2. Ulcerative Colitis Medications By Disease Location

Disease Location	Typical Medication	Usual Dose Range	Notes
Proctitis	Mesalamine supp	bid to tid	Active disease
		every 3rd night	Maint. remission
	Cortisone foam	hs or bid	Active disease
		every 3rd night	Maint. remission
Distal colitis			
Topical	Mesalamine enemas	qhs	Active disease
		every 3rd night	Maint. remission
	Hydrocortisone enemas	qhs	Active disease
		every 3rd night	Maint. remission
Systemic	Sulfasalazine	4-6 g daily	Active
		2 g daily	Remission
	Dipentum	2-4 g daily	Active
		1-2 g daily	Remission
	Asacol	2-4.8 g daily	Active
		2.4 g daily	Remission
	Prednisone	Variable	Not for maintenance
Extensive colitis			
	Sulfasalazine	4-6 g daily	Active
		2 g daily	Remission
	Dipentum	2-4 g daily	Active
		1-2g daily	Remission
	Asacol	2-4.8 g daily	Active
		2.4 g daily	Remission
	Prednisone	Variable	Not for maintenance
Refractory disease	6-MP	50-125 mg daily	CBC monthly, hold dose for wbc <3.7, notify GI
	Azathioprine (Imuran)	50-150mg daily	CBC monthly, hold dose for wbc< 3.7, notify GI

Table 3. Crohn's Disease Medications By Disease Location

Disease Location	Typical Medication	Usual Dose Range	Notes
Stomach	Prilosec	20 mg daily	? efficacy.
	Prednisone	Variable	Not for maintenance
Duodenum	Pentasa	3.2-4.8 g daily	*
	Prednisone	Variable	Not for maintenance
Jejunum/ileum	Pentasa		*
	Asacol	3.2-4.8 g daily	*
	Prednisone	Variable	Not for maintenance
Colon	Asacol	3.2-4.8 g daily	*
	Prednisone	Variable	Not for maintenance
	Dipentum	3.2-4.8 g daily	*
	Metronidazole	10-20mg/kg/day	Active disease only. Monitor for sxs of peripheral neuropathy
	Sulfasalazine	4-6 g daily	Active disease only, not helpful for maintaining remisson
Fistulous disease			
	Metronidazole	10-20mg/kg/day	Monitor for sxs of peripheral neuropathy
	6-MP	50-125 mg daily	CBC monthly, hold dose for wbc <3.7, notify GI
	Azathioprine (Imuran)	50-150mg daily	CBC monthly, hold dose for wbc< 3.7, notify GI
	ciprofloxacin	1 gram daily	?efficacy
Refractory disease			
	6-MP	50-125 mg daily	CBC monthly, hold dose for wbc <3.7, notify GI
	Azathioprine (Imuran)	50-150mg daily	CBC monthly, hold dose for wbc< 3.7, notify GI

*Dose needed to treat active disease and acheive remission should be continued for maintenance.

Table 4. Associated Concerns

Checklist for Inflammatory Bowel Disease	**Yes**	**No**	**Action (for any "yes" response)**
Malabsorption			
Ileitis-B12 deficient?			Replace
Anemia-iron deficient?			Replace
Neoplasia risk			
UC			
left-sided colitis >12-15years?			GI referral
extensive colitis > 8-10 years?			GI referral
Crohn's			
Colon disease > 12-15 years?			GI referral
Associated Conditions			
PSC			GI follow-up annually